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DEVELOPMENT OF TUBERCULOSIS IN ADULT LIFE

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MINNEAPOLIS

When the words phthisis and consumption were employed by Hippocrates, they designated exactly what the physician saw when he made the diagnosis. Later, when it was known that the disease usually exists for a long time before the body visibly wastes away, the word tuberculosis was coined. This word is all inclusive and in the light of recent observations may be applied to the disease from the time the neutrophils first phagocytose tubercle bacilli until the death of the host results.

Until recently physicians were unwilling to make a diagnosis of tuberculosis until clinical manifestations were present, such as symptoms and abnormal physical signs, with roentgen findings, or until the laboratory methods revealed tubercle bacilli in the sputum or pleural effusion or elsewhere. Although diagnoses based on these criteria were made far earlier in the course than those in the time of Hippocrates and for many centuries thereafter, they usually indicated that the disease had been present for a long time, and in from 80 to 85 per cent of the cases the disease had reached a moderate or far advanced stage.

It is now known that the first attack of the tubercle bacillus is on the neutrophil, since it is this cell which first phagocytoses the bacillus. The polysaccharide content of the bacillus is toxic to the neutrophil, and although this is a single cell, the destruction in the body begins with the "illness and death" of the neutrophil. Therefore, the first skirmish results in defeat for the human body. No sooner do the toxic effects to

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(Footnote continued on next page)

the neutrophils become manifest, however, than the second line of defense makes its appearance. This consists of the monocytes, which surround the ill, dead and disintegrating neutrophils and ingest them and the tubercle bacilli which they contain. There is nothing in the chemistry of the tubercle bacillus which destroys the monocytes. However, the phosphatide content of the bacillus apparently causes their conversion into epithelioid cells. While some bacilli may die in the epithelioid cells, others not only remain alive but also multiply. Later, lymphocytes are attracted to the site of the developing tubercle.

It is possible that the differential leukocyte counts of the peripheral blood may be found to give some evidence of the developing tubercle. An attempt is now being made to determine whether the increase in neutrophils, followed by an increase in monocytes and later by an increase in lymphocytes, is sufficient to be demonstrated in the peripheral blood in a recently exposed subject who has actually become infected with tubercle bacilli. While such changes in the leukocytes are not specific for tuberculosis, in the absence of other conditions which cause them and in the presence of recent exposure they are suggestive when demonstrated.

The waxes of the tubercle bacilli stimulate the proliferation of fibroblasts, while their acetone-soluble fat causes proliferation of all local connective tissue cells. This results in the laying down of fibrous tissue around the periphery of the tubercle. In many cases lime salts are deposited in the small caseous centers and in the capsule, while in about 25 per cent true bone is laid down in the capsule.¹ Thus, a temporary victory is won by the body, but unfortunately the bacilli remain alive, and the fibrous and even the bony capsules surrounding them may rupture or later be resorbed,¹ thus setting free these living and virulent micro-organisms.

After a period of from three to seven weeks² of tubercle formation enough tuberculo-protein has been liberated by the bacilli, through disintegration and other processes, to result in sensitization of the tissues to this substance. Up to this time there has been no way of determining the presence of tubercle bacilli and tubercle formation in the body. There are no symptoms or abnormal physical signs, the tuberculin test is negative and roentgenograms give no aid. Indeed, before sensitization appears, tubercle formation is sufficiently under way to control the tubercle bacilli at least temporarily and often for the lifetime of the patient.

Oregon Tuberculosis Association, Portland, Ore., April 2, 1936, and the California Tuberculosis Association, Sacramento, Calif., on April 3, 1936.

1 Sweany, Henry. Studies on the Pathogenesis of Primary Tuberculous Infection, *Am Rev Tuberc* **27** 559, 1933.

2 Wallgren, Arvid. Primary Pulmonary Tuberculosis in Childhood, *Am J Dis Child* **49** 1105 (May) 1935.

After sensitization is established a most valuable diagnostic aid is available, in that tuberculin or pure tuberculo-protein applied to an abrasion of the skin or administered intracutaneously results in a reaction which reveals the presence of sensitization to tuberculo-protein. As far as is known, there is nothing which is taken into the body which results in such sensitization except tubercle bacilli which have caused tubercle formation.³ Thus, a positive reaction to tuberculin is highly diagnostic of the first infection type of tuberculosis somewhere in the body.

At one time it was thought that the first infection type of tuberculosis is established in a high percentage of children before the period of adolescence. This probably was true in many places and apparently is still true in a few densely populated centers, such as Philadelphia.⁴ However, throughout the greater part of the United States and in some other parts of the world the campaign against tuberculosis in man and animals has so greatly reduced or controlled the number of cases of communicable tuberculosis in both man and animals that large numbers of children now grow to adult life without having had the first infection type of tuberculosis. Indeed, in a few places the situation has been so completely reversed that, although formerly from 90 to 95 per cent of the young adults had been infected, now only from 5 to 10 per cent react positively to the tuberculin test.⁵ In Norway Heimbeck⁶ found that 52 per cent of the students entering a school of nursing reacted negatively to the test. A similar percentage of negative reactions was found in other groups in the same age period. In the part of the French army recently tested as many as 42 per cent of the soldiers reacted negatively to tuberculin.⁷ In our testing of student nurses during the period of probation in recent years we have frequently found that less than 10 per cent react positively to the tuberculin test.⁸ Thus, large numbers of persons are now reared through infancy and child-

3 Baldwin, E. R. Studies in Immunity to Tuberculosis. I. Hypersusceptibility or Anaphylaxis, *J. M. Research* **22** 189, 1910. Krause, Allen K. Factors in the Pathogenesis of Tuberculosis, *Am. Rev. Tuberc.* **18** 208, 1928.

4 Hetherington, H. W., McPhedran, F. M., Landis, H. R. M., and Opie, Eugene L. A Survey to Determine the Prevalence of Tuberculous Infection in School Children, *Am. Rev. Tuberc.* **20** 421, 1929.

5 Fourth Annual Report of the Tuberculosis Committee of the American Student Health Association, *Journal-Lancet* **55** 350 (June 1) 1935.

6 Heimbeck, J. Immunity to Tuberculosis, *Arch. Int. Med.* **41** 336 (March) 1928.

7 Tuberculin Testing of the French Army, Paris letter, *M. Rec.* **142** 524, 1935.

8 Myers, J. A., Diehl, H. S., and Lees, H. D. The Student Nurse and Tuberculosis, *J. A. M. A.* **102** 2086 (June 23) 1934.

hood and pass into adult life without having even the first infection type of tuberculosis

With the decrease in the incidence of positive reactors among children and young adults in many parts of this country, there has occurred a decrease in the morbidity and mortality from tuberculosis. It has been pointed out that in some schools of nursing in recent years all the students who reacted negatively to tuberculin as probationers reacted positively at the time of graduation.⁹ If all uninfected students become infected during the course of their training, it seems probable that those who were infected previous to training are reinfected. Therefore, with approximately 100 per cent of the students contaminated with tubercle bacilli during the course of their training, one must expect the incidence of demonstrable lesions, which subsequently develop, to be much higher than in a general population, in which not more than from 10 to 30 per cent of the young adults have been infected with tubercle bacilli. Where actual observations have been made this has been found to be true.

Great fear has been expressed by some authors that since the so-called protective doses of tubercle bacilli did not reach the bodies of these young adults in the period of infancy or childhood, when they become infected in schools of nursing and medicine, very serious forms of disease will develop.¹⁰ Others have asked what actually occurs in such uninfected subjects if they become contaminated with tubercle bacilli for the first time in adult life. Does a more severe form of tuberculosis develop, and do the lesions respond to treatment in a different manner than those of persons who were first infected earlier in life?

In schools of nursing and medicine, where the students come in contact with tuberculous patients, in the absence of an adequate technic for dealing with contagious disease, there has in recent years been presented an opportunity to study the development of tuberculosis in young adults that is rarely equaled by animal experimentation, except that in experimental work it is possible to control the dosage and to kill an animal at any time in order to make a postmortem study. Since 1927 we have seen many students of nursing and medicine become contaminated with tubercle bacilli for the first time, the evidence of this contamination being a positive reaction to tuberculin which appeared after the student was exposed to tuberculous patients. In many of these students there has been no other manifestation of tuberculosis as yet. They are classified as having the first infection type of disease somewhere in their bodies, with the location undetermined. Among this

9 Geer, Everett K. Tuberculosis Among Nurses, *Arch Int Med* 49 77 (Jan) 1932. Heimbeck.⁶ Myers, Diehl and Lees.⁸

10 Factors in the Falling Death Rate from Tuberculosis, editorial, *Ann Int Med* 9 1154 (Feb) 1936.

group we have observed subjects in whom after the tissues had become sensitized lesions developed in such locations or to such an extent that they could be demonstrated by roentgenograms or other phases of the examination. None of these subjects has been observed for longer than nine years and many of them for a much shorter period. A few have been briefly reported on elsewhere¹¹. In others who reacted positively to the tuberculin test when they entered, we have also seen lesions develop. Therefore, we have grouped these subjects on the basis of the tuberculin reaction, the type of lesion which subsequently developed and other factors.

GROUP 1

In the subjects in group 1 the reaction to tuberculin changed from negative to positive under our observation, and erythema nodosum appeared.

CASE 1—In September 1931 an 18 year old freshman in a school of nursing reacted negatively to tuberculin. She again showed a negative reaction in September 1932. In February 1933 she had erythema nodosum, following which the tuberculin test was found to be strongly positive. There have been no other developments and apparently she is in excellent health at present.

CASE 2—In January 1932 a freshman in a school of medicine reacted negatively to the tuberculin test. In March 1933 and February 1934 he still showed a negative reaction. Roentgen films of the chest in January 1932 and February 1934 showed no evidence of disease. He was on a service for tuberculous patients for three weeks in January 1935. On February 4 the tuberculin test was positive. In March 1935 he had erythema nodosum. In December 1936 a tuberculous abscess developed in the soft tissues beneath the clavicle on the right side. In February 1936 films showed no evidence of disease in either lung.

Thus, only two of the persons we have observed have come to our attention with erythema nodosum. This is in sharp contrast with the observations made by a number of authors who have reported erythema nodosum as a common development among those whose tissues have recently become sensitized to tuberculoprotein. We are cognizant of the fact that erythema nodosum is not always caused by sensitiveness to tuberculoprotein and that a number of other conditions may be responsible. However, when it appears, it is sufficiently suggestive to lead one to make a careful examination for tuberculosis. We have not regarded erythema nodosum as a clinical form of tuberculosis.

GROUP 2

In the subjects in group 2 the reaction to tuberculin changed from negative to positive, and a primary focus was demonstrated roentgenographically. No other lesions were demonstrated.

11 Myers, J. A. (a) Recent Facts on Transmission of Tuberculosis, J. A. M. A. **97** 316 (Aug. 1) 1931, (b) Types of Tuberculous Lesions Found in Chests of Students of Nursing and Medicine, Am. Rev. Tuberc. **28** 93, 1933.

CASE 1—In November 1928 a freshman medical student aged 22 reacted negatively to the tuberculin test. In 1931 the reaction to tuberculin was still negative. Roentgen films of the chest in March 1930 and subsequently, including Jan 27, 1932, showed no evidence of disease. This student was working in a service for tuberculosis patients from Dec 18, 1931, to Feb 18, 1932. In February 1932 the tuberculin test was positive. A roentgenogram made on April 25 showed a small shadow in the first interspace on the right, as well as a similar shadow in the first interspace on the left. Twenty subsequent roentgen examinations, the last on Dec 16, 1935, showed that the lesions had varied slightly but that throughout this period there had been some decrease in the size of the shadow. There were no symptoms, and no treatment was given.

CASE 2—In September 1929, on beginning a five year nursing course, at the age of 20, a student showed a negative reaction to the tuberculin test. The reaction to tuberculin and the roentgenograms continued to be negative on periodic examinations. From Aug 15 to Sept 15, 1933, she was assigned to a service for tuberculous patients. On Jan 23, 1934, the reaction to the tuberculin test was positive, and a roentgenogram revealed evidence of definite infiltration at the level of the first interspace on the left. Numerous films made after that, the last on Jan 3, 1936, showed a gradual decrease of the shadow, with possible beginning calcification in the hilar region of the left lung. At no time was there any symptom of pulmonary tuberculosis. No treatment was given.

CASE 3—In November 1928 a 23 year old freshman in a school of medicine reacted negatively to the tuberculin test. On periodic examinations the reaction continued to be negative. In December 1931 he gave intimate care to a diabetic patient who was in a far advanced stage of unsuspected pulmonary tuberculosis. In January 1932 the student showed a positive reaction to the tuberculin test. Roentgen films made in February 1932 revealed a definite infiltration in the upper lobe of the left lung, extending from the apex to the level of the second rib. The shadow remained unchanged until September 1932, when there was some evidence of resolution. On Dec 19, 1933, there was marked clearing of the shadow. There had been no symptoms of tuberculosis, and no treatment had been given.

CASE 4—In February 1928 a premedical student aged 22 reacted negatively to the tuberculin test. The reaction was periodically negative thereafter, including September 1931. Roentgenographic examination of the chest in January 1931 and January 1932 showed no evidence of disease. The student was assigned to a special service for tuberculous patients from Sept 15 to Sept 30, 1931. Three weeks later the reaction to the tuberculin test was strongly positive. At this time roentgen films of the chest revealed no evidence of disease. On May 30, 1932, there was evidence of infiltration within the circle of the first rib in the first interspace on the right side. There had been no symptoms of tuberculosis, and no treatment had been given.

CASE 5—In October 1928 a 20 year old freshman in a school of medicine showed a negative reaction to the tuberculin test. The test was not repeated. There was said to have been a normal roentgenogram in 1930. In June 1931 a roentgenogram revealed evidence of pulmonary infiltration in the apex of the right lung and in the first interspace and in the first and second interspaces on the left. A roentgen film on Feb 2, 1932, showed no change in the shadows, while those made in September 1934 and in January and June 1935 showed almost complete disappearance of the shadows. This man is now practicing medicine and apparently is in excellent health.

CASE 6—In January 1931 a junior medical student aged 24 showed a negative reaction to the tuberculin test. During the next year he roomed with an intern who had a draining sinus from tuberculous cervical nodes. In February 1932 the student showed a positive reaction to the tuberculin test. A roentgenogram of the chest made on Dec 29, 1931, showed evidence of a small density at the level of the third rib on the left side near the periphery. Subsequent films showed evidence of calcification in this area. The shadow was unchanged in a film made on Oct 9, 1935. No symptoms had developed, and no treatment had been given.

CASE 7—In September 1931 a 19 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. Roentgen films of the chest showed no evidence of disease in October 1931. The reaction to tuberculin continued to be negative in October 1932 and October 1933. Three weeks after being assigned to a service for tuberculous patients in September and October 1934 the student showed a strongly positive reaction to the tuberculin test. In September 1934 the roentgen film was still negative, but on May 1, 1935, there was evidence of infiltration in the upper lobe of the left lung. On July 8 there was a slight decrease in the extent of the shadow. All films subsequent to this examination, the last being made on Jan 7, 1936, revealed practically no change in the shadow. No symptoms developed, and no treatment was given.

CASE 8—In the fall of 1931 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test. In June 1935, after being graduated from the nursing school, the patient showed a negative reaction to the tuberculin test. Roentgen films made in February 1934 showed no evidence of disease. In May 1935 she gave intimate care as a special duty nurse to two tuberculous patients. On September 27 the reaction to the tuberculin test was positive. In October there was evidence of infiltration in the upper lobe of the left lung. All subsequent films, the last on Jan 22, 1936, showed no change in the shadow. No symptoms developed, and no treatment was given.

CASE 9—In September 1930 a 17 year old first year premedical student reacted negatively to the tuberculin test. The reaction was negative in April 1933 and in February 1934. The student came in contact with tuberculous patients when he was working in a service for patients with diseases of the nose and throat. He was not assigned to a special service for tuberculous patients. In February 1935 the reaction to the tuberculin test was strongly positive. On February 19 there was a small area of disease present in the lower portion of the upper lobe of the right lung. On May 21 a film showed a definite increase in the extent of the shadow in the right lung. On June 15 the shadow had decreased somewhat in size. In October and November 1935 and in January 1936 films showed no change in the appearance of the shadow. No symptoms developed and no treatment was given.

CASE 10—In the fall of 1933 a 21 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. Roentgen films which had been taken in the fall of 1933 showed no evidence of disease. During the fall the student had some contact with tuberculous patients. About Feb 14, 1934, she experienced pain in the left side of the chest, and a film showed an area of infiltration at the level of the first and second interspaces on the left side. This was thought to be a small area of pneumonia. The tuberculin test was not repeated at this time. On February 22 a roentgen film showed no change in the shadow. On March 16 the film showed some decrease in the size of the shadow. The student became suspicious that she had tuberculosis, and on March 14 had a tuberculin test made privately. At this time she showed a strongly positive reaction. No symptoms developed, and no treatment was given.

CASE 11—In September 1930 a 24 year old graduate nurse, while taking a course in public health nursing, reacted negatively to the tuberculin test. A roentgen film of the chest showed no evidence of disease. In July 1932 the reaction to the tuberculin test was positive. On July 17 a roentgen film revealed definite evidence of infiltration in the first and second interspaces on the right side. On August 17 there was a slight decrease in the size of the shadow. On October 20 the shadow was unchanged. No symptoms developed, and no treatment was given.

CASE 12—In October 1931 a 22 year old junior in a school of nursing showed a negative reaction to the tuberculin test. The reaction remained negative throughout her nursing course. On Jan 14, 1933, a roentgen film revealed no evidence of disease. In February the student worked in a service for tuberculous patients. Three months later the tuberculin test was strongly positive. On April 28, 1933, roentgen films of the chest were negative. On August 30, 1935, a roentgen film revealed definite evidence of infiltration in the first and second interspaces near the periphery on the left side. In November 1935 and January 1936 roentgen films showed no change in the shadow. Slight pain over the upper part of the left side of the chest was the only symptom.

CASE 13—In 1924 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test. In January 1933 she registered for graduate work in nursing, and the tuberculin test was found to be definitely positive. On February 13 there was evidence of infiltration involving the first and second interspaces on the right side. In April, June and September 1933 roentgen films revealed no change in the shadow. No symptoms developed, and no treatment was given. On March 1936 a film showed almost complete disappearance of the shadow. The nurse is now in excellent health.

CASE 14—In 1929 a 19 year old second year premedical student reacted negatively to the tuberculin test. In November 1933 his roommate was found to have a far advanced stage of pulmonary tuberculosis. A roentgen film of the student's chest showed no evidence of disease in December 1933. On June 14, 1934, there was an area of infiltration in the left lung at the level of the third rib, midway between the periphery and the hilus. There was evidence also of definite infiltration in the hilar region. The student was institutionalized for five months. Roentgen films made on Jan 2, 1935, showed a definite decrease in the extent of the shadow. Further decrease was observed on Feb 18, 1935, and April 22, 1935. On Feb 20, 1935, phrenic exeresis was performed. On June 17 the shadow was small. A roentgen film on Jan 20, 1936, showed almost complete disappearance of the shadow.

CASE 15—In September 1931 a 19 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. In May 1933 the tuberculin test was strongly positive. The student was assigned to a service for tuberculous patients from Sept 15 to Nov 1, 1934. Roentgen films of the chest made on Sept 14, 1934, and March 26, 1935, showed no evidence of disease. On July 31, 1935, definite infiltration appeared in the apex and the first interspace on the left side. The shadow remained unchanged in films made in August, September and October 1935 and on Feb 20, 1936. She was under treatment for four and one-half months. No symptoms developed.

CASE 16—In 1928 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test. She worked in a service for tuberculous patients in the spring of 1932. Through October 1933 reaction to the tuberculin test remained negative. In July 1934 the reaction was definitely positive, and an area of infiltra-

tion was present in the second interspace near the periphery on the left. Elevation of the temperature and fatigue were noted. Strict rest in bed for a few weeks was ordered. At present the nurse is able to work full time.

CASE 17—In September 1933 a 23 year old freshman in a school of nursing reacted negatively to the tuberculin test. A roentgen film of the chest made on Oct 19, 1933, showed no evidence of disease. On April 22 she reacted positively to the tuberculin test. A roentgen film of the chest on May 8 showed evidence of a small area of infiltration at the level of the second interspace on the right side. Films made on June 18 and July 23 showed an increase in the size of the shadow. The only treatment was rest in bed. In March 1936 no change in the shadow was apparent.

CASE 18—In September 1934 a 25 year old freshman in a school of medicine reacted negatively to the tuberculin test. Subsequently a fraternity brother who was a graduate of a medical school lived in the same house, and while there it was found that he had pulmonary tuberculosis in a communicable form. On Jan 14, 1936, the student showed a positive reaction to the tuberculin test, and roentgenograms showed evidence of infiltration in the apex of the left lung and in the first interspace. A roentgen film on Feb 24, 1936, showed no change in the size of the shadow.

CASE 19—In September 1930 a 19 year old first year premedical student reacted negatively to the tuberculin test. In April 1933 the reaction to the test was positive. On July 24, 1933, and Feb 26, 1934, roentgenograms of the chest showed no evidence of disease. On Feb 27, 1935, there was definite evidence of infiltration in the subclavicular region on the right side. Periodic films made over the next several months showed no change. On Dec 27, 1935, there was a slight decrease in the size of the shadow.

CASE 20—In September 1932 a 19 year old freshman in a school of nursing reacted negatively to the tuberculin test. The reaction continued to be negative at periodic examinations. Roentgenograms of the chest on Aug 11, 1934, showed no evidence of disease. The student worked in a service for tuberculous patients in October and November 1934, immediately after which the tuberculin test was definitely positive. On May 2, 1935, an x-ray film showed no evidence of disease. On Sept 26, 1935, there was definite evidence of infiltration in the left lung, extending from the region of the hilus into the second and third interspaces. The shadows showed no change in October and November 1935 but were slightly decreased in extent in February 1936. No symptoms developed and no treatment was given.

CASE 21—In September 1929 a 19 year old freshman in a school of medicine reacted negatively to the tuberculin test. The reaction continued to be negative in February 1930, February 1931 and February 1932. Roentgenograms of the chest in January 1930, January 1931 and March 1932 showed no evidence of disease. The student was assigned to a special service for tuberculous patients from Oct 3 to 16, 1932. The reaction to the tuberculin test was still negative in February 1933, but in August 1934 it was positive. Roentgenograms made in June 1934, after slight pain had been noted in the chest and the temperature had reached 100 F each day for ten days, revealed an area of infiltration only in the first interspace on the left side. Films made on Aug 13, 1935, and compared with the films taken during the previous year showed a gradual decrease in the extent of the shadow in the left lung. Films made on Dec 4, 1935, showed that there had been no change since August.

In a few cases in this group it has been impossible to determine with certainty that the shadows represented only the first infection type of tuberculosis, because the tuberculin testing was not always done with sufficient frequency. We regard any lesion that appears soon after the tissues are sensitized as representing the first infection type of the disease. However, if a year or more has elapsed between the making of the tuberculin tests, there has been ample time between the last negative and the first positive reaction for the first infection type of disease to develop and also for the reinfection type to make its appearance.

There is nothing characteristic about the shadow produced by either type with regard to density, location and other features. From the shadow alone it is impossible to differentiate between the first infection type of tuberculosis, the reinfection type of tuberculosis, pneumonia, abscess and other processes in the early course of development. It is only when the tuberculin tests have been carefully administered and the reactions interpreted with sufficient frequency or when the lesions have been observed for a sufficiently long time that it is possible to differentiate between the first infection and the reinfection type of tuberculosis.

Not all lesions of the first infection type of tuberculosis attack the lungs, and among those which do there are many that do not become sufficiently large or produce enough reaction around them to cast shadows which can be visualized by the naked eye on the x-ray film. Indeed, in the majority of young adults who become infected, it is impossible by any phase of the examination actually to locate the lesions. In this respect young adults do not differ from infants and children who become contaminated with tubercle bacilli, in whom it has been shown that under most ideal examinations it is rare to locate the lesion in as many as 25 per cent of those reacting positively to the tuberculin test at any one time¹². Nevertheless, a definitely positive reaction to the tuberculin test is accurate evidence of the presence of tubercle formation somewhere in the body.

Obviously, since a lesion of the first infection type of tuberculosis is microscopic in the beginning a considerable period of time is required for it to grow to sufficient size to cast a shadow which can be visualized on an x-ray film. About the time the tissues become sensitized to tuberculo-protein or soon after in a small percentage of cases an inflammatory area appears around the lesion. When this area is sufficiently extensive to cast a shadow that can be visualized on the x-ray film, it is usually homogeneous in appearance over a period of many weeks or months, after which it begins to disappear. Wallgren,² Chown and

12 Harrington, F. E. Childhood Type Tuberculosis. A Report of Ten Years of Activity, 1921-1931, Lymanhurst School for Tuberculous Children, Minneapolis, The Board of Public Welfare, 1932.

Medovy,¹³ Reichle¹⁴ and many others have called attention to these shadows as they appear in infancy and childhood. Attention has been called to the appearance of such lesions among young adults, particularly among students of nursing and medicine or recent graduates in these professions, by a number of workers, notably Heimbeck,¹⁵ Rist¹⁶ and Geer.¹⁷ Rigler¹⁸ has made a study of the period of time which elapses between exposure and the attainment by a lesion of sufficient size to cast a clearly visible shadow on the x-ray film.

The nature of the inflammatory reaction around the focus has been discussed elsewhere.¹⁹ As is the case among children, none of these lesions has shown evidence of cavitation. The subjects who have been observed for a sufficiently long time have shown a definite reduction in the size of the shadows, and in some cases no evidence of disease remains. In other cases shadows remain which are interpreted as strands of fibrous tissue, and occasionally lime deposits make their appearance at the site of a previous shadow.

In the majority of these cases there have been no noticeable symptoms. In the occasional case there has been slight pain in the chest or a mild elevation of the temperature. The general absence of symptoms or the occasional presence of mild symptoms of short duration is in conformity with the findings in infants and children with the first infection type of disease.²⁰ Physical signs are usually entirely lacking.

Those subjects whom we have observed throughout the course of the disease have received no treatment. A few of the subjects who have come under the observation of other physicians have undergone hospitalization and interruption of the phrenic nerve. However, the ultimate results are apparently the same either with or without treatment. This does not differ from what has been found to be true for infants and children with the first infection type of tuberculosis, even

13 Chown, Bruce, and Medovy, Harry. Pulmonary Tuberculosis in Childhood, *Canad M A J* **29**:364, 1933.

14 Reichle, H S. Resolving Exudates in Pulmonary Tuberculosis of Childhood, *Am J Dis Child* **45**:307 (Feb), **46** 969 (Nov) 1933.

15 Heimbeck, J. Ueber Infektion und Vakzination bei Tuberkulose, *Med Klin* **29** 1731, 1933.

16 Rist, E. Opening of a Sanatorium for Students, *M Rec* **142** 522, 1935.

17 Geer, Everett K. Primary Tuberculosis Among Nurses, *Am Rev Tuberc* **29**:88, 1934.

18 Rigler, Leo G, and Exner, Frederick B. The Latent Period in the Roentgen Diagnosis of Pulmonary Tuberculosis, *J A M A* **102** 1750 (May 26) 1934.

19 Myers, J A. The First-Infection Type of Tuberculosis. Its Preallergic and Postallergic Stages of Development, *Am Rev Tuberc* **34** 317, 1936.

20 Myers, J A, Harrington, F E, Stewart, C A, and Wulff, Marjorie. First-Infection-Type Tuberculosis. Its Treatment and Prognosis, *Am Rev Tuberc* **32** 631, 1935.

when the lesions are extensive²¹ Thus, in our experience the subject who has avoided infection through infancy and childhood and becomes infected in adult life shows the first infection type of lesions, and these take the same benign course as similar lesions which develop in infants and children The first infection type of tuberculosis begins to develop in tissues that are not sensitized to tuberculo-protein The defense mechanism, consisting of leukocytes, connective tissue cells and other factors, usually causes the tubercle bacilli to be well surrounded and under at least temporary control before sensitization occurs This reaction is far less intense than when reinfection begins development on sensitized tissues, as shown experimentally by Lemon²²

GROUP 3

In the subjects in group 3 the reaction to tuberculin changed from negative to positive The primary parenchymal lesions were demonstrable roentgenographically in some cases and nondemonstrable in others Pleural effusion also developed

CASE 1—In February 1930 a 22 year old freshman in a school of medicine reacted negatively to the tuberculin test The reaction continued to be negative through October 1932 After the student had worked in a service for tuberculous patients the reaction to tuberculin became positive On Feb 20, 1933, pleural effusion was present on the right side, although the roentgenogram made on Feb 10 had shown a normal picture In June 1933 the effusion had completely absorbed, and there appeared only evidence of thickening of the pleura In August 1933, in addition to evidence of diaphragmatic pleurisy, there was a small area of involvement in the parenchyma of the upper lobe of the right lung In October 1933 this shadow had not changed The lesion persisted through the remainder of 1933 and 1934 but could not be visualized in June 1935 This woman is now working full time as a resident physician in a hospital

CASE 2—In January 1929 a 24 year old sophomore medical student reacted negatively to the tuberculin test The reaction continued to be negative through Jan 5, 1931, when a roentgenogram showed no evidence of disease He was assigned to a special service for tuberculous patients from Dec 6, 1930, to Jan 5, 1931, and again from March 8 to 18, 1931 The reaction to the tuberculin test was markedly positive on March 14, 1931 The roentgenogram made at that time showed no evidence of disease On April 20 the roentgenogram revealed an area of parenchymal infiltration near the periphery in the second interspace on the right side On June 9 a large effusion was present in the right pleural cavity On October 26 the effusion had nearly disappeared, but the parenchymal lesion appeared unchanged Numerous subsequent films revealed obliteration of the right costophrenic angle On April 17, 1933, and Feb 12, 1936, the parenchymal shadow was observed to be sharply outlined and considerably reduced in size This man is now working full time as a physician in government service

21 Myers, J A Treatment, Prognosis and Prevention of First Infection Type of Tuberculosis, *Journal-Lancet* 56 24, 1936

22 Lemon, W S, and Montgomery, L G Pleural and Pulmonary Lesions Resulting from Intrapleural Injection into Rabbits of *Mycobacterium Tuberculosis*, *J Thoracic Surg* 3 612, 1934

CASE 3—In November 1926 a 20 year old sophomore medical student reacted negatively to the tuberculin test. The reaction was negative throughout her entire medical course. In May 1929 the reaction became strongly positive after she had worked in a service for tuberculous patients as an intern. A roentgenogram of the chest showed a small area of infiltration in the pulmonary parenchyma near the periphery, at the level of the second interspace on the right. In May 1930 a large pleural effusion was present on the right side and persisted for several months. After that numerous roentgenograms of the chest showed obliteration of the costophrenic angle on the right. On Feb 24, 1936, a film showed evidence of probable beginning calcification in the region of the parenchymal shadow. This woman is now married and is practicing medicine. Apparently she is in excellent health.

CASE 4—In October 1928 a 23 year old junior medical student reacted negatively to the tuberculin test. In July 1929 the reaction was positive, a pleural effusion was present on the right side and a small parenchymal infiltration was present in the apex of the right lung. The student was hospitalized from July 17 to Nov 14, 1929. Subsequent roentgenograms, taken through 1935, have shown evidence of thickening of the pleura over the base of the right lung, and the area of disease in the apex has become small. This man is now practicing medicine and apparently is in good health.

CASE 5—In February 1930 a 21 year old freshman in a medical school reacted negatively to the tuberculin test. In February 1931 he showed a positive reaction to the tuberculin test. A roentgenogram of the chest made on Jan 20, 1930, and another made on Jan 30, 1931, showed no evidence of disease. A film made on May 5, 1931, showed pleurisy with effusion on the right side. There was a small area of infiltration at the level of the third interspace near the periphery on the right side. After the patient had spent three months at rest in bed the effusion had disappeared. The only remaining evidence of pleurisy through many subsequent examinations was thickening of the pleura over the base of the right lung. The lesion in the pulmonary parenchyma showed no change through the remainder of 1931, 1932 and 1933, including April. This man is now practicing medicine and is apparently well.

CASE 6—In September 1930 a 19 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. A roentgenogram of the chest on Sept 6, 1932, showed nothing abnormal. From Sept 15 to Nov 1, 1932, she worked in a service for tuberculous patients. On May 15, 1933, the reaction to the tuberculin test was positive, and on May 19 she had pleurisy with effusion on the right side. Practically all the fluid had absorbed by September 15. On July 6, 1933, as the fluid was absorbing, a small area of infiltration appeared in the right lung at the level of the second and third interspaces. This shadow appeared practically unchanged on films taken on September 15 and November 22. However, on November 22 a small area of infiltration was present in the first interspace on the left side. On Jan 25, 1934, the shadow in the right lung had slightly increased in size. On July 13 the shadow in the left lung was not visible, while that in the right lung had become smaller. On November 7 both shadows were visible. On Jan 7, 1935, the shadow in the right lung was sharply outlined, and that in the left lung was barely visible. On July 1 the shadow in the right lung had increased somewhat in extent, while that in the left lung was not visible.

CASE 7—In January 1932 an 18 year old freshman in a college of science, literature and arts reacted negatively to the tuberculin test. During part of the time he was in college he was associated with a friend who had tubercle bacilli in the sputum. In June 1935 the student had pleurisy with effusion on the left side.

and a definite area of infiltration in the upper lobe of the left lung. At this time the reaction to the tuberculin test was positive. Since then the student has been hospitalized.

CASE 8—In March 1933 a 27 year old sophomore in a school of medicine showed a negative reaction to the tuberculin test. The reaction was negative also in 1934 and in January 1935. On April 6, 1934, roentgenograms of the chest were entirely clear. The student was assigned to a service for tuberculous patients from Jan to Feb 10, 1935. In April 1935 he complained of pain in the chest. On May 1 the reaction to the tuberculin test was positive, and pleural effusion was present. The effusion had entirely disappeared by Aug 20, 1935. On December 11 there remained only evidence of slight thickening of the pleura on the left side. No treatment was given. He is now working full time as an intern and apparently is in excellent health.

CASE 9—In 1930 a 24 year old second year premedical student showed a negative reaction to the tuberculin test. In 1931 and 1932 the reaction was still negative. Roentgenograms of the chest in February 1931 and 1932 showed no abnormality. On Feb 21, 1933, the reaction to the tuberculin test was positive, but roentgenograms of the chest again showed nothing abnormal. The student was assigned to a service for tuberculous patients for three weeks in October 1934. Roentgenograms in March 1935 showed a normal chest, but films made in July 1935 showed evidence of pleurisy with effusion on the left side. The student was kept strictly at rest in bed until Oct 1, 1935. On November 15 a roentgenogram revealed only evidence of previous pleurisy, with no effusion. No symptoms of a pathologic condition of the parenchyma could be visualized. This man is now practicing medicine and apparently is in good health.

CASE 10—In May 1930 a 20 year old second year premedical student reacted negatively to the tuberculin test. The reaction was again negative in February 1931, February 1932 and February 1933. Roentgenograms of the chest in January 1931 and February 1932 revealed no evidence of disease. The student was assigned to a service for tuberculous patients for three weeks, beginning June 18, 1933. At that time the reaction to the tuberculin test was positive. Roentgenograms of the chest in February 1934 and December 1934 showed no evidence of disease. On Dec 8, 1934, roentgenograms showed definite evidence of pleural effusion on the right side. The effusion persisted over several months, after which it absorbed, so that on Dec 18, 1935, there was no evidence of adhesions or other remnants of the pleurisy. The chest appeared essentially normal. This man is now working full time as a resident physician.

CASE 11—In September 1929 a 19 year old freshman in a school of nursing reacted negatively to the tuberculin test. During part of August and September she was exposed to a patient who had tuberculosis in a communicable form. In October the reaction to the tuberculin test became strongly positive, but a roentgenogram showed no evidence of disease. On Nov 25, 1930, pleural effusion was present on the right side. After several months the fluid absorbed, and numerous roentgenograms made subsequently, the last in September 1935, showed evidence of thickening of the pleura over the base of the right lung with obliteration of the costophrenic angle. This woman is now working full time as a nurse and apparently is in good health.

CASE 12—In September 1930 a 20 year old junior in a school of nursing showed a negative reaction to the tuberculin test. In October 1931 the reaction was still negative. In June 1932, after being exposed to tuberculosis, the student showed a positive reaction to the tuberculin test. Roentgenograms made on June

3 and Aug 18, 1932, and March 8, April 27, Aug 1 and Dec 1, 1933, showed no evidence of disease. On Jan 15, 1934, pleural effusion was present on the left side. By March 7, 1934, the effusion had disappeared, and there was evidence of thickening of the pleura with adhesions over the base of the left lung. On July 30, 1934, there was no change. This woman was last seen on Aug 3, 1934, when she accepted a position in another state, and she was apparently in good health.

CASE 13—In September 1932 a 22 year old student in a school of nursing reacted negatively to the tuberculin test. Roentgenograms of the chest made on Sept 22, 1932, showed no evidence of disease. From October 1 to November 15 she was assigned to a service for tuberculous patients. On Jan 31, 1933, the reaction to the tuberculin test was positive and pleural effusion was present on the left side. The effusion persisted through February but was definitely diminished, as shown by a roentgenogram made on March 14. By Jan 26, 1934, the fluid had completely disappeared, and there was no evidence of its previous existence by way of thickening of the pleura or obliteration of the costophrenic angle.

CASE 14—In September 1931 a 19 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. The reaction was again negative in October 1932. Roentgenograms of the chest in October 1932 showed no evidence of disease. In February 1933 reaction to the tuberculin test was positive, but roentgenograms of the chest showed no evidence of disease. Because of pain over the upper part of the left side of the chest, roentgenograms were made on Feb 17, 1933, and these showed slight evidence of infiltration in the upper lobe on the left side. On March 6 pleural effusion was easily demonstrated on the left side. On April 4 the fluid had practically disappeared, but there was obliteration of the left costophrenic angle. Numerous roentgenograms since then, the last on June 6, 1935, have shown the development of a Ghon tubercle in the region of the previous infiltration on the left side, but a small area of infiltration has appeared in the extreme apex of the left lung. There have been no symptoms at any time after the pleural effusion disappeared. This woman is now working full time as a nurse and apparently is in good health.

CASE 15—In 1925 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test. She was graduated from the school of nursing in 1928. From 1928 to 1932 she worked in a service for tuberculous patients. In June 1932 pleurisy with effusion developed on the right side, and the reaction to the tuberculin test was found to be positive. After four months the patient entered a sanatorium, where she was treated for eighteen months. In February 1936 a roentgenogram of the chest showed no evidence of disease in either lung.

CASE 16—In September 1930 a 21 year old sophomore in a school of nursing reacted negatively to the tuberculin test. The reaction was still negative just before she entered a service for tuberculous patients from July 15 to Aug 17, 1933. The test was not administered again until April 1934, when she was registered for a course on public health nursing, the reaction was then definitely positive. X-ray films of the chest on July 13 and Sept 14, 1933, had showed no evidence of disease. On April 21, 1934, there was definite roentgen evidence of pleurisy at the base of the left lung, but no fluid could be demonstrated. By Jan 18, 1935, all evidence of pleurisy had disappeared.

CASE 17—In September 1931 a 21 year old freshman in a school of nursing reacted negatively to the tuberculin test. The reaction was still negative on Sept 23, 1932. Roentgenograms of the chest in September 1932 showed no evidence of pulmonary disease. In January 1935, as a student in public health nursing, she showed a positive

reaction to the tuberculin test On Jan 28, 1935, roentgenograms of the chest revealed no evidence of disease On April 10 a roentgenogram showed evidence of a small effusion in the right pleural cavity The amount of fluid increased until a large effusion was present on April 16 On May 2 there was a considerable decrease in the amount of fluid Further decrease was observed on May 10 In March 1936 there was no evidence of pleurisy

CASE 18—In March 1935 a 20 year old freshman in a school of agriculture reacted negatively to the tuberculin test In 1934, when he was a high school student, the reaction to the test was negative On March 5, 1936, evidence of pleural effusion on the right side was noted At this time the reaction to the tuberculin test was definitely positive, but the source of exposure was unknown

We regard pleurisy with effusion as a reinfection form of tuberculosis which develops from the focus of the first infection The tissues are highly sensitized to tuberculo-protein through the development of the primary lesion, and bacilli are easily transmitted to the lymph channels of the visceral pleura from the lesions which often lie near the periphery of the lung The appearance of fluid in the pleural cavity is usually preceded by pain, and friction sounds may be elicited for a few days When effusion begins to make its appearance and ordinary anteroposterior roentgenograms will not demonstrate it with certainty, Rigler's²³ posture method is of great aid When the effusion becomes larger, it is usually possible to recover tubercle bacilli from smears of centrifugated fluid or by culture and inoculation methods There is usually a rise in temperature, and it often increases until it reaches 102 or 103 F The fever may be present for only a few days, or it may persist for several weeks In the occasional case fever is slight or absent, and no pain is experienced

In the earlier years of our work, we aspirated nearly all the larger effusions and in some cases introduced air into the pleural cavity More recently, however, aspiration has been practiced only when the effusion was so large as to displace the mediastinum, when pressure symptoms were present or when fever had persisted for an unduly long time We have discontinued the use of air in the pleural cavity unless a reinfection type of lesion can be demonstrated in the lung A period of rest in bed is usually indicated while symptoms are present, although some of our patients who for various reasons did not have such periods of rest in bed controlled the disease without complications In none of this group of patients have we seen any complication, such as empyema

After the effusion absorbs there may remain definite evidence of thickening of the pleura, diaphragmatic adhesions and partial or complete obliteration of the costophrenic angle Again no abnormal finding

²³ Rigler, Leo G Roentgen Diagnosis of Small Pleural Effusions, J A M A 96 104 (Jan 10) 1931

remains, the excursion of the diaphragm is normal, and from no phase of the examination, including roentgenograms, is one able to detect any evidence of the previously existing pleurisy.

We have seen pleurisy with effusion follow rather closely the development of the first infection type of tuberculosis in infants and children, but it appears to occur more frequently in young adults who have recently been infected. It is possible that this is only apparent, because the infant or child may not be able to call attention to the pain and other symptoms, or the fever is thought to be due to ordinary respiratory infection and hence an adequate examination is not made while the effusion is present. In a group of 4,148 children who showed a negative reaction to the tuberculin test, 89 showed some evidence of pleural change. Although 30 of these children had visible interlobar pleural shadows, between either the upper or the lower and the middle lobe of the right lung, we no longer regard this as a significant finding in all cases. In 40 there was definite evidence of diaphragmatic adhesions and pleurisy over the base of one or both lungs. In 17 there was evidence of thickening of the pleura over an entire lung, suggestive of an earlier existence of pleural effusion. In 3 there was evidence of interlobar or encapsulated effusion. In another group of 1,782 children with a slightly positive reaction to tuberculin, 25 showed evidence of pleural changes, 4 of whom had only visible interlobar pleural shadows. In another group of 2,615 children with a markedly positive reaction to tuberculin, 145 showed evidence of changes in the pleura, 55 of whom had only visible interlobar pleural shadows. The remaining 90 had definite pleural changes, such as diaphragmatic adhesions and thickening of the pleura over an entire lung, and 10 had pleurisy with effusion at the time of examination.^{11a}

Among the young adults reported on in this paper, more careful observations were made by the students themselves, as well as those in charge of the examinations, than for the group of children. Hence, slight symptoms, such as pain in the chest were usually reported early. One must not overlook the possibility that by the time adult life is reached foreign material may have so accumulated or resulted in such changes in the lymphatic vessels as to decrease their efficiency, thus retarding the flow of lymph and giving tubercle bacilli which reach the lymph channels in the visceral pleura a longer opportunity to gain a foothold.

GROUP 4

In the subjects in group 4 the reaction to tuberculin changed from negative to positive, and clinical pulmonary tuberculosis later made its appearance, with or without a demonstrable primary focus or pleurisy with effusion.

CASE 1—In September 1932 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test and continued to do so through March and September 1933. A roentgenogram of the chest in July 1933 showed no evidence of disease. The reaction to the tuberculin test was positive in March 1934. On April 16 a roentgenogram showed evidence of slight infiltration in the base of the right lung. On May 1 this area had definitely increased in size. After a slight pulmonary hemorrhage and the finding of tubercle bacilli in the sputum in May 1934 artificial pneumothorax treatment was instituted, with the patient ambulatory. This student was graduated in February 1936 and is apparently in good health.

CASE 2—In January 1931 a 17 year old first year premedical student reacted negatively to the tuberculin test. In May 1933 he had a pulmonary hemorrhage. There had been no known exposure to tuberculosis. In June 1933 he reacted positively to 1 mg of tuberculin. On May 24 there was infiltration extending from the shadow of the clavicle to the level of the fourth rib. On May 26 the sputum contained tubercle bacilli. On June 1 artificial pneumothorax was instituted, with the student ambulatory. He has continued in medical school and apparently is in good health.

CASE 3—In March 1932 a 20 year old freshman medical student reacted negatively to the tuberculin test and continued to do so through February 1934. Roentgenograms of the chest in March 1932 showed no evidence of disease. In November 1934 the reaction to the tuberculin test was strongly positive. Roentgenograms of the chest in February 1934 and March 1935 showed no evidence of disease. In July 1935, while working as an intern, he had a pulmonary hemorrhage. A roentgenogram on July 17 showed evidence of a large infiltration in the medial portion of the upper lobe of the right lung, with evidence of cavitation. Strict rest in bed was immediately instituted, and artificial pneumothorax was begun on the right side on July 28. The patient is still in bed but apparently is making an excellent recovery.

CASE 4—In February 1928 a 28 year old junior in a school of dentistry reacted negatively to the tuberculin test. In April 1931 pleurisy with effusion developed on the left side. He was kept at rest in bed for several months. On Jan 25, 1932, evidence of pleurisy with effusion was found on the right side. A small amount of fluid was still present on June 9, and there had also appeared a small area of infiltration in the first interspace on the left side. Numerous roentgenograms made since that time have shown no change in the parenchymal shadow, and there remains evidence of thickening of the pleura over the bases of both sides. At the present time this man is practicing dentistry and is apparently in good health.

CASE 5—In September 1930 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test and continued to do so through June 1931. In May 1932 the reaction to the tuberculin test was positive. She worked in a service for tuberculous patients from Dec 31, 1932, to Feb 15, 1933. On April 20, 1932, a roentgenogram showed no evidence of disease. On December 29 roentgenograms revealed a small area of infiltration in the second interspace near the periphery on the left side. On May 8, 1933, the area of infiltration had extended into the third interspace on the left side, and there was some indication of beginning cavity formation. Artificial pneumothorax was then instituted on the left side, and the patient was treated in a sanatorium until Aug 21, 1935. She continues to receive artificial pneumothorax treatment and is apparently in good health.

CASE 6—In September 1932 a 22 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. Roentgenograms of the chest made on October 28 showed no evidence of disease. On May 15, 1933, the reaction to the tuberculin test was positive. Roentgenograms of the chest made on July 29, 1933, Feb 28, 1934, and July 14, 1934, showed no evidence of disease. On Nov 14, 1934, an area of infiltration was present at the level of the first interspace on the left. The student worked in a service for tuberculous patients from Nov 15, 1934, to Jan 2, 1935. On Jan 2, 1935, roentgenograms revealed no change in this shadow. At this time there was a questionable area of infiltration in the right lung at the level of the third interspace. On January 7 the shadow in the left lung remained unchanged, as well as the questionable area in the right lung. On March 4 no change was evident. On April 5 the shadow in the left lung showed slight evidence of an increase in size, while that in the right lung had extended from the third to the fourth interspace. The patient was then hospitalized. In August there was a considerable increase in the extent of the shadow, and artificial pneumothorax was instituted. In December empyema developed and is still being treated by the aspiration method.

CASE 7—In 1928 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test and continued to do so through her entire nursing course. After graduation in 1931 she did private duty nursing. In June 1935 she accepted a position in a hospital where there was considerable contact with tuberculous patients. In October 1935 roentgenograms revealed evidence of infiltration in the first and second interspaces on the right side and from the apex of the left lung to the fourth rib. On November 12 the reaction to the tuberculin test was definitely positive. This was the only test that had been administered since her graduation in 1931. No symptoms developed but strict rest in bed was instituted. On Feb 7, 1936, there was evidence of a slight decrease in the extent of the shadow.

CASE 8—In September 1932 an 18 year old freshman in a school of pharmacy reacted negatively to the tuberculin test. No roentgenograms were made. In November 1935 he complained of pain in the right side of the chest. A roentgenogram made on November 21 revealed evidence of extensive disease with cavity formation in the upper lobe of the right lung. Artificial pneumothorax was instituted with the patient ambulatory.

CASE 9—In January 1928 a 20 year old freshman in a school of medicine reacted negatively to the tuberculin test. In February 1930 the test was still negative. He worked in a service for tuberculous patients from April 9 to 20, 1931. A lesion with cavity formation developed at the base of the right lung while he was serving his internship. This lesion was controlled by artificial pneumothorax.

CASE 10—In October 1931 a 20 year old junior in a school of nursing showed a negative reaction to the tuberculin test. In October 1930 roentgenograms of the chest revealed no evidence of disease. In August and September 1933 the student worked in a service for tuberculous patients, and soon afterward the reaction to the tuberculin test became positive. A roentgenogram of the chest in October 1933 showed no evidence of disease. The student was graduated from the school of nursing in June 1933 and then married. A normal infant was born in September 1934. The woman undertook private duty nursing in May 1935 and worked continuously until January 1936, apparently being in excellent health. Early in January 1936 she observed two nodules on the calf of the left leg. She consulted a dermatologist,

who suspected the presence of tuberculosis. Roentgenograms revealed infiltration in the upper lobe of the left lung at the level of the first interspace and a similar area of disease in the upper lobe of the right lung. No symptoms referable to the lung developed, but strict rest in bed was instituted.

CASE 11—In 1930 a 19 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. Soon after working in a service for tuberculous patients in June, July and August 1933 she showed a strongly positive reaction. Roentgenograms of the chest at that time showed no evidence of disease. However, in November and December 1933 the patient suffered considerably from pains in the chest. A roentgenogram made on Nov 12, 1935, revealed evidence of infiltration in the left lung, extending from the apex to the fourth rib, in the right lung there was infiltration in the second interspace near the periphery. Adhesions prevented the administration of artificial pneumothorax. Strict rest in bed was instituted.

CASE 12—In 1928 a 19 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. Subsequent tests showed a negative reaction until she had spent six weeks in a service for tuberculous patients, beginning in September 1930. The reaction to the test was then definitely positive, but a roentgenogram showed no evidence of disease. On Oct 29, 1933, while at work, she had a frank pulmonary hemorrhage. Examination revealed definite evidence of disease, with probable cavity formation in the upper lobe of the right lung. Artificial pneumothorax was instituted with the patient ambulatory. She is now apparently in good health.

CASE 13—In April 1928 a 21 year old second year student in a school of nursing was given a tuberculin test. Although the record of this test was lost, the nurse stated that the reaction was negative. Roentgenograms of the chest in April 1928 showed no evidence of tuberculosis. After working in a service for tuberculous patients she showed a definitely positive reaction to the tuberculin test in October 1929. On Jan 23, 1934, a roentgenogram revealed definite evidence of infiltration extending from the apex to the third rib on the left side. Artificial pneumothorax was instituted with the patient ambulatory, but adhesions prevented the complete collapse of the area of disease. This woman is now apparently in good health.

CASE 14—In September 1929 a 20 year old junior in a school of nursing showed a negative reaction to the tuberculin test. On October 7 a roentgenogram of the chest showed no evidence of disease. On July 24, 1931, there was evidence of thickening of the pleura on the left side, but no fluid could be demonstrated. On August 8 a slight area of infiltration was visualized in the second interspace on the left side, but the reaction to the tuberculin test was reported as negative. On November 5 another area of infiltration was visualized in the fourth interspace. On December 23 the shadows had increased somewhat in extent. Strict rest in bed was instituted, and the shadows showed no change by June 28, 1932. Rest in bed was continued, but on April 3, 1933, a definite increase in the size of the shadow was observed. In May artificial pneumothorax was attempted without success. Through July and September 1933 there was no change in the shadow. On Jan 22, 1934, there was a slight decrease in the extent of the shadows in the left lung, but a small area of infiltration was visualized at the level of the third interspace on the right. At this time, the reaction to tuberculin was strongly positive. In October 1935 and on Jan 7, 1936, there was no evidence of change in the shadows.

CASE 15—In January 1933 an 18 year old freshman in a school of nursing reacted negatively to the tuberculin test Six months later she still showed a negative reaction In March 1934 she reacted positively A roentgenogram made on May 24 showed no evidence of disease Another, made on Dec 18, 1935, revealed evidence of considerable infiltration scattered throughout the upper lobe of the right lung and diffusely throughout the left lung Tubercle bacilli were present in the sputum Strict rest in bed was instituted

CASE 16—In September 1931 a 19 year old freshman in a school of nursing reacted negatively to the tuberculin test and continued to do so through October 1932 Roentgenograms of the chest in December 1932 showed no evidence of disease In March 1933 the reaction to the tuberculin test was positive Roentgenograms of the chest showed no evidence of disease in April 1934 On Feb 7, 1935, there was a definite area of infiltration occupying the apex and the first interspace on the left side Artificial pneumothorax was instituted, with the patient ambulatory, and there has been no further development

CASE 17—In October 1929 a 20 year old freshman in a school of nursing showed a negative reaction to the tuberculin test Roentgenograms also were negative After caring for a tuberculous patient, she showed a positive reaction to the test in September 1930 In July 1931 there was a definite area of infiltration in the first and second interspaces on the right and a smaller area in the first and second interspaces on the left After she had rested in bed for a year roentgenograms showed evidence of a marked decrease in the extent of the shadows She then returned to school and was later assigned to the care of a patient who was being treated for fracture and who had unsuspected communicable pulmonary tuberculosis In March 1933 the shadow in the left lung had definitely increased in size In April there was evidence of a small cavity in the lesion in the left lung Artificial pneumothorax was attempted, but adhesions prevented complete collapse of the lung However, there was sufficient collapse to justify continuation of the treatment By May 1934 oblitative adhesions had markedly reduced the pleural space, but the shadows in the left lung were definitely decreased in size, and those in the right lung were barely visible In January 1935 there was no change in the shadows In November 1935 an acute illness occurred which in the beginning the family physician diagnosed as influenza However, he later found that the lower half of the left lung was involved by tuberculous pneumonia, and there was a definite increase in the extent of the shadows previously visualized On the right side the small shadow remained unchanged

CASE 18—In December 1927 a 20 year old freshman in a school of medicine reacted negatively to the tuberculin test and continued to do so through December 1930 From Nov 20 to Dec 1, 1930, he worked in a special service for tuberculous patients Roentgenograms of the chest in November 1930 showed no evidence of disease The next test, administered in April 1931, showed a definitely positive reaction During this month the supraclavicular lymph nodes on the left side became enlarged, and biopsy revealed tuberculosis In April 1931 a roentgenogram revealed evidence of infiltration in the apex of the left lung In May and June this shadow remained unchanged, and an area of infiltration appeared in the apex of the right lung By October 3 the shadow in the left lung had increased in extent In August tuberculous epididymitis developed In February 1932 he had tuberculous peritonitis and was hospitalized from April 1932 to June 1933 He is now employed in a hospital and apparently is in good health

CASE 19—In November 1927 a 23 year old sophomore in a school of medicine reacted negatively to the tuberculin test and continued to do so until the spring

of 1929, before he began working in a service for tuberculous patients. No further tests were administered until July 1933, when a definitely positive reaction was present. At this time a roentgenogram revealed no evidence of disease. Numerous films made subsequently showed no definitely abnormal shadows until May 21, 1934, when there was an area of infiltration present in the upper lobe of the right lung. No change was then observed until June 1, 1935, when an improvement was noted in the area of infiltration in the upper lobe of the right lung, but a small area of infiltration had appeared in the upper lobe of the left lung. On November 13 there was evidence of infiltration throughout the entire upper lobe on the left side, and the infiltration in the upper lobe of the right lung had increased. On Jan 6, 1936, no change could be observed in the shadows. On February 22 there was an increase in the extent of the shadows in the left lung, and tubercle bacilli were present in the sputum. Artificial pneumothorax was instituted on February 29.

CASE 20—In November 1927 a 21 year old sophomore medical student reacted negatively to the tuberculin test. In January 1930 the reaction was positive. From Dec 6, 1930, to Jan 5, 1931, and again from March 8 to 18, 1931, he worked in a special service for tuberculous patients. Roentgenograms of the chest on Dec 30, 1930, showed no evidence of disease. After graduation he worked on a full time basis and apparently was in excellent health until December 1935, when roentgenograms revealed definite evidence of infiltration extending from the apex to the third rib on the right side. He is now at strict rest in bed.

CASE 21—In October 1929 a 22 year old freshman in a school of medicine reacted negatively to the tuberculin test. Roentgenograms in January 1930 and January 1931 showed no evidence of disease. He worked in a service for tuberculous patients from Dec 11 to 23, 1932. The reaction to the tuberculin test was positive in February 1933. On February 20 a small area of infiltration appeared in the fourth interspace on the right side. In May the area of infiltration had increased somewhat in size, and there was evidence of enlargement of the peritracheal lymph nodes on the right side. In October 1933 a moderately large pleural effusion was present on the right side. The fluid had disappeared by December 19, and there remained evidence of thickening of the pleura and obliteration of the costophrenic angle. On Nov 19, 1934, the shadow in the fourth interspace on the right side was unchanged, but a definite area of infiltration had appeared in the apex of the right lung. In January 1935 he had a pulmonary hemorrhage. Since then he has been in a sanatorium and has undergone interruption of the phrenic nerve on the right side.

CASE 22—In December 1929 a 24 year old junior in a school of medicine showed a negative reaction to the tuberculin test. He then left school to work. The next test was administered in January 1932 and showed a definitely positive reaction. Roentgenograms of the chest on March 2 and 10 showed evidence of a Ghon tubercle and calcified mediastinal lymph nodes on the right side. There was evidence also of an infiltration in the first interspace on the right side. Because of symptoms of abdominal involvement exploratory laparotomy was performed on March 15, 1932, and revealed extensive tuberculosis of the peritoneal cavity. Large caseous nodules were present and extended over the large bowel. The upper portion of the abdominal cavity seemed to show the greatest involvement, but there was no portion which was free from the process. Death occurred on May 19, 1932.

CASE 23—In February 1930 a 23 year old junior in a school of medicine showed a negative reaction to the tuberculin test. Roentgenograms made in 1926 showed no evidence of disease. In February 1931 the reaction to the tuberculin

test was positive after he had been working in a service for tuberculous patients from January 5 to 16. Roentgenograms of the chest at this time were negative. In June 1932 there was a large pleural effusion on the right side. When the effusion absorbed, there was evidence of a small infiltration in the third interspace on the right side near the periphery. No further symptoms developed until November 1933, when a profuse pulmonary hemorrhage occurred, followed by massive atelectasis of the left lung. When the atelectasis disappeared, there was evidence of a large area of tuberculous pneumonia, which was treated by artificial pneumothorax. Later, empyema developed, and after this had become sufficiently chronic, thoracoplasty was recommended. On Jan 17, 1936, fatal pulmonary hemorrhage occurred before thoracoplasty had been attempted.

CASE 24—In October, 1932, a 20 year old freshman in a school of nursing showed a negative reaction to the tuberculin test. In March 1933 the reaction to the test was positive. On July 24, 1933, a small area of infiltration was visualized in the first and second interspace on the right side. In February 1934 the shadow previously observed was not visualized. On March 13, immediately after the development of symptoms similar to those of pneumonia, a roentgenogram showed a homogeneous dense shadow involving the greater part of the upper lobe on the right side. On April 9 and 14 there was evidence that the disease had spread to the base of the left lung. Artificial pneumothorax was instituted about May 1, after which all symptoms disappeared. On June 15 the left lung was under a good state of collapse, and the right lung appeared clear. This patient then returned to her home and continued treatment with her family physician. Empyema later developed, and she died on May 25, 1935.

CASE 25—In May 1933 a 28 year old clerk in the office of a board of education reacted negatively to the tuberculin test. The summer of 1933 was spent in a home with a patient who had tuberculosis in a communicable form. On Jan 10, 1934, the clerk had a small pulmonary hemorrhage. A careful examination revealed small areas of infiltration in the apex and first interspace on the right side and in the apex of the left lung. The reaction to the tuberculin test was positive. The patient was immediately hospitalized.

It is possible that an occasional patient in this group had only the first infection type of lesion, because the tuberculin tests were not administered with sufficient frequency to permit differentiation with certainty. However, in the majority of cases sufficient time elapsed between the finding of the positive reaction to tuberculin and the development of the lesion to assure with a reasonable degree of certainty that the lesion was of the reinfection type. In some of our cases after the development of sensitiveness to tuberculin the location of the first foci of infection could not be determined. Neither did pleurisy with effusion nor any other evidence of disease become manifest until the reinfection type was detected. For example, in case 12 there was a positive reaction to tuberculin in 1930, but it was not until 1933, almost three years after her graduation, that a pulmonary hemorrhage occurred—the first manifestation of clinical disease.

Case 20 is a similar example. He was first found to react positively to the tuberculin test in January 1930, but it was not until approximately six years later that he was ill with pulmonary tuberculosis. In others

we have seen the first infection type of focus appear in the lung soon after the reaction to the tuberculin test became positive, and later the reinfection type of disease was seen to develop, as in case 17. In still others, after the reaction first became positive, we have been able to demonstrate the location of the first infection type of lesion and have seen pleural effusions develop and finally the reinfection type of disease, as in cases 21 and 23. Only 3 of these patients have died. In cases 23 and 24 tuberculous pneumonia developed, followed by empyema. In case 24 death was due to empyema, in case 23 it was due to pulmonary hemorrhage. In case 22 severe and fatal abdominal tuberculosis developed. In each of these 3 students we followed the evolution of tuberculosis from the time of exposure to tuberculous patients until death occurred from resulting lesions.

With modern methods of treatment in most of our cases the lesions are at least temporarily under control. Fortunately, through periodic roentgen examinations of subjects who show a positive reaction to tuberculin it is now possible to detect the location of chronic pulmonary lesions of the reinfection type long before symptoms appear. When such lesions are detected and are proved to be progressive, treatment should be instituted at once. Artificial pneumothorax with the patient ambulatory²⁴ is proving satisfactory in many cases, particularly when the disease is unilateral, and has been administered to a few patients in this group. Because of the long interval between the time of exposure to tuberculous patients, resulting in sensitization of the tissues to tuberculo-protein, and the actual development of the chronic reinfection type of lesion, most students when graduated from schools of nursing and medicine apparently are in good health, but when they are traced over a sufficiently long period, it is not unusual to find that clinical disease has developed. However, the lesions are no more severe and respond just as well to treatment as the lesions which develop in adult life among persons who were infected in infancy or childhood.

GROUP 5

In the subjects in group 5 the reaction to tuberculin was positive when our observation began, but no evidence of clinical disease could be demonstrated. Later, reinfection forms of tuberculosis made their appearance.

CASE 1—In September 1930 an 18 year old freshman in a school of nursing reacted positively to a full milligram of tuberculin. Roentgenograms in March and August 1931 showed no evidence of disease. In June 1932 a roentgenogram

²⁴ Myers, J. A. Collapse Therapy and the Ambulatory Patient, *J Thoracic Surg* **3** 175, 1933. Myers, J. A., and Levine, Ida. Artificial Pneumothorax in the Treatment of Progressive Minimal Pulmonary Tuberculosis, *Am Rev Tuberc* **31** 518, 1935, Artificial Pneumothorax With Particular Reference to the Ambulatory Patient, *J Thoracic Surg*, to be published.

revealed evidence of infiltration in the first interspace near the periphery on the left side. In July there was no change in the shadow. In September the shadow had slightly increased. In February 1933 there was a marked decrease in the size of the shadow. In April and September only slight evidence of disease remained in this area. However, in February 1934 the extent of the shadow had definitely increased, and evidence of infiltration was present in the apex of the right lung. By January 1935 improvement was again shown in the left lung, and the right remained unchanged. No change was observed in either lung in subsequent roentgenograms through December 1935.

CASE 2—In December 1928 a 20 year old student nurse reacted positively to the tuberculin test. Roentgenograms of the chest showed visible interlobar pleura on the right side but no evidence of disease in either lung. In November 1932, after registering for a course in public health nursing, she showed definite evidence of infiltration in the apex of the left lung. In January 1933 there was no change in the appearance of the shadow. In September 1933 this woman began working as a nurse and has continued on a full time basis.

CASE 3—In September 1930 a 25 year old junior in a school of dentistry reacted positively to the tuberculin test. On Feb 26, 1931, a large pleural effusion was noted on the right side. By June 1931 the effusion had absorbed, and there remained only evidence of thickening of the pleura and diaphragmatic adhesions on the right side. Roentgenograms made in 1932, 1933 and 1934 showed no change in his condition.

CASE 4—In November 1927 a 21 year old sophomore in a medical school reacted positively to the tuberculin test. He had been exposed to a brother who died of tuberculosis in 1923. Roentgenograms of the chest on March 19, 1929, showed no evidence of disease. He worked in a service for tuberculous patients from Jan 27 to Feb 9, 1930. In May 1934 roentgenograms revealed a small area of infiltration in the lower lobe of the right lung. On June 30 he had a pulmonary hemorrhage. At this time there was evidence of cavitation in the lower lobe of the right lung, and he was institutionalized from July 16 to October 19. Artificial pneumothorax was instituted on August 27. He changed climate from January to October 1935. Since then he has been practicing medicine and apparently is in good health.

CASE 5—In January 1931 a 47 year old freshman in a school of medicine showed a positive reaction to the tuberculin test. Roentgenograms on Jan 20, 1931, and Feb 1, 1932, revealed no evidence of disease. On Feb 28, 1933, there was definite evidence of infiltration in the left lung extending from the apex to the third rib, as well as an area of infiltration in the first interspace on the right side. In April and June 1933 roentgenograms showed no change in the shadows.

CASE 6—In March 1932 a 21 year old freshman in a school of nursing reacted positively to the tuberculin test. Roentgenograms of the chest at that time and again in August showed no evidence of disease. In November there was evidence of a small infiltration in the apex of the right lung. In March 1933 the shadow in the right lung was unchanged. In the left lung at the level of the second interspace was a fairly large area of infiltration. On April 15, 1933, the shadow in the right lung was unchanged, but that in the left lung had definitely increased, and there was evidence of cavity formation. The sputum contained tubercle bacilli. Artificial pneumothorax was instituted on the left side, and the patient was sent to a sanatorium. In April 1935 tuberculous pneumonia developed in the right lung, after which pneumothorax was discontinued on the left side, later, partial collapse was instituted on the right side. On Feb 25, 1936, intrapleural pneumolysis was performed on the right side.

CASE 7—In September 1932 a 21 year old freshman in a school of nursing reacted positively to the tuberculin test. Roentgenograms of the chest on Nov 1, 1932, and Dec 29, 1934, showed no evidence of disease. The student worked in a special service for tuberculous patients from Jan 1 to Feb 15, 1935. On September 24 a roentgenogram revealed an area of infiltration in the upper lobe of the left lung. On November 12 and December 10 the shadow showed no change. On Jan 6 and Feb 27, 1936, roentgenograms revealed no change in the shadow.

CASE 8—In October 1932 a 20 year old freshman in a junior college reacted positively to the tuberculin test. No roentgenogram was made until Jan 29, 1935, when there was evidence of calcium deposits in the hilar region of the right lung. There were no other abnormal findings. During the next year a sister living in the home was found to have tuberculosis in a communicable form. Roentgenograms made on Dec 30, 1935, showed in addition to the lime deposits evidence of infiltration extending from the apex to the second rib on the right side.

CASE 9—In 1932 a 24 year old freshman in a medical school showed a positive reaction to the tuberculin test. There was a history of tuberculous cervical adenitis in childhood, and a remaining scar was present in the cervical region on the right. A roentgenogram revealed evidence of a Ghon tubercle in the right lung, with calcified lymph nodes in the hilar region. There was evidence of diaphragmatic adhesions on the right side. On Dec 6, 1933, a diagnosis of tuberculosis of the left kidney and tuberculosis of the left epididymis was made. Nephrectomy was performed on June 6, 1934. Examination of the chest in May 1935 showed only calcifications, as reported in 1932.

CASE 10—In April 1932 a 21 year old junior in a school of nursing reacted positively to the tuberculin test. At that time roentgenograms of the chest revealed no evidence of disease. On May 6, 1933, a roentgenogram showed evidence of pulmonary tuberculosis involving the upper lobes of both lungs, with cavitation in the apex of the right lung. Artificial pneumothorax was instituted with the patient ambulatory, after which she worked for some time as a nurse. She was then married and has given birth to a normal infant.

CASE 11—In September 1929 a 19 year old freshman in a school of medicine reacted positively to the tuberculin test. On Jan 9, 1930, roentgenograms of the chest showed no evidence of disease. On March 6 pleural effusion was present on the right side and persisted through March, when the student left school. By March 17, 1931, the effusion had completely absorbed, and there was evidence of thickening of the pleura over the base of the right lung. On Feb 8, 1935, infiltration had appeared in the apex of the right lung and in the subclavicular region. Infiltration was present in the apex of the left lung and in the first and second interspaces. In May there was no change in the shadows. On Feb 10, 1936, the extent of the shadow in the right lung had increased, while that in the left lung showed no change. There were no symptoms at any time except when the effusion was present.

CASE 12—On Sept 28, 1932, a 19 year old sophomore student in a school of nursing reacted positively to the tuberculin test. On Nov 1, 1932, and April 26, 1933, roentgenograms of the chest revealed no evidence of disease. On Sept 19, 1934, an infiltration was present in the first interspace on the left side. This showed no change since roentgenograms were made in October 1934. In November 1934 there was a slight increase in the extent of the shadow. On March 19, 1935, the phrenic nerve on the left side was temporarily interrupted because of an increase in

the shadow On June 9, after a small hemoptysis occurred, artificial pneumothorax was instituted on the left side The patient is now making satisfactory progress

CASE 13—In March 1932 a 19 year old freshman in a school of nursing reacted positively to tuberculin A roentgenogram made on April 8 showed no evidence of disease She worked in a service for tuberculous patients from Nov 8 to Dec 24, 1934 On Nov 13, 1934, roentgenograms showed infiltration involving the apex and first interspace on the left side The shadow did not change through 1935, the last examination being made on Nov 22, 1935

CASE 14—In September 1930 a 17 year old freshman in a school of science, literature and arts reacted positively to the tuberculin test, having been exposed to her father, who died of tuberculosis in 1932 Records elsewhere showed that the reaction to the tuberculin test was positive in 1926 and that periodic roentgenograms of the chest had revealed no evidence of disease On May 16, 1933, a roentgenogram revealed an area of infiltration involving the apex and first interspace on the right side Tubercle bacilli were recovered from the sputum Artificial pneumothorax with the patient ambulatory was instituted on July 5 She has since been graduated and has registered in the graduate school Apparently she is in good health

CASE 15—In October 1933 a 30 year old teacher reacted positively to the tuberculin test A roentgenogram of the chest taken on November 4 revealed evidence of calcium deposits in the second interspace on the left On Jan 10, 1934, after a small pulmonary hemorrhage occurred, definite evidence of tuberculous pneumonia involving the entire upper field of the left lung was noted

The question often arises as to whether in those students who react positively to the tuberculin test on admission to schools of nursing and medicine clinical forms of tuberculosis develop while they are in school or soon after graduation, and, if so, whether the lesions differ materially from the lesions of those who become sensitized to tuberculo-protein during the course of their training In group 5 are included fifteen subjects, mostly students, who when first examined reacted positively to the tuberculin test but who showed no roentgen evidence of disease or only evidence of primary foci In all of them, either while in school or soon after graduation, clinical forms of tuberculosis developed One had pleurisy with effusion (case 3), another had renal tuberculosis (case 9) and the others had pulmonary lesions The sixth patient was the only member of her class who reacted positively to the test in the first year of nursing Within approximately a year she had pulmonary tuberculosis, with cavity formation, and there were tubercle bacilli in the sputum She has since had bilateral artificial pneumothorax and intrapleural pneumolysis and at the present time is seriously ill As far as we have been able to observe, the lesions which developed in this group have not differed in intensity or response to treatment from the lesions of those in whom clinical disease developed after the reaction to the tuberculin test had become positive while the subjects were under our observation

One must take into consideration the small number of positive reactors who were admitted to these schools. It seems probable that some selection has been practiced among the students who already had been contaminated when they entered. For example, in the communities in which the subjects were reared other girls and boys also had become contaminated with tubercle bacilli. Those in whom pleurisy with effusion or clinical lesions developed while they were in high school in all probability were not advised by their family physicians or their parents to enter schools of nursing or medicine. Thus, for the most part only those who had previously been contaminated and who had shown no external manifestations of tuberculosis entered such schools.

GROUP 6

In the cases in group 6 no previous tuberculin tests had been made but the roentgenographic findings were negative. Later, extensive pulmonary tuberculosis developed.

CASE 1—In December 1927 a 22 year old graduate student reported for examination because it had been found that her roommate had had far advanced tuberculosis six months previously. The tuberculin test was not administered. A roentgenogram of the chest made on December 5 revealed no evidence of disease in either lung. On March 3, 1931, when this woman was teaching, a roentgenogram revealed only a Ghon tubercle formation in the upper lobe of the right lung. On March 17, 1932, a roentgenogram revealed extensive disease in the upper field of the right lung, with evidence of cavity formation. On April 15 artificial pneumothorax with the patient ambulatory was instituted, and the treatment has been continued to the present time.

CASE 2—On May 24, 1929, a 20 year old student in a college of science, literature and arts showed no roentgenographic evidence of disease of the lungs. The tuberculin test was not administered. He entered a law school and completed the course. On May 28, 1935, roentgenograms of the chest revealed evidence of extensive disease with cavitation involving nearly the entire left lung. In the right lung the area of infiltration extended from the apex to the third rib, with cavitation at the level of the second rib. Strict rest in bed was instituted.

CASE 3—In November 1928 a 19 year old student nurse had roentgenograms of the chest made which were reported as negative. No tuberculin test was administered. In August 1931 she was found to have a far advanced stage of pulmonary tuberculosis involving both lungs, with tubercle bacilli in the sputum. Strict rest in bed and later bilateral artificial pneumothorax were instituted.

CASE 4—In October 1926 a 23 year old freshman in a school of dentistry showed no roentgen evidence of disease of the lungs. The tuberculin test was not administered. During the next year he was in intimate contact with a friend who had tuberculosis. On Oct 20, 1927, there was a definite area of infiltration in the second interspace on the right. On April 25, 1931, a roentgenogram revealed evidence of disease involving the first and second interspaces on the right side, with cavity formation. Tubercle bacilli were present in the sputum. Artificial pneumothorax treatment with the patient ambulatory was instituted on July 3, 1931, and was discontinued on Oct 21, 1935. Now this man is apparently in good health and is enrolled as a medical student at the age of 33.

The statement is occasionally made that during the teen age period roentgenograms of the chest will reveal evidence of any disease which may cause illness at a later time in life. However, in each of the four cases (the respective ages being 22, 29, 19 and 23 years) in group 6 the roentgenograms were entirely clear, yet several years later in each case an advanced stage of pulmonary tuberculosis developed. It now appears obvious that tuberculosis may develop in persons of any age. Any one who escapes infection as a child may become infected through contact exposure, and clinical disease may develop at any subsequent time.

In the accompanying table we have partially summarized the course of events in the 85 cases reported in this paper. It will be observed that neither meningitis nor miliary disease occurred among our patients.

Data

No. of Cases	Reaction to Tuberculin		X Ray Findings	
	Initial	Subsequent	Initial	Final
2	Negative	Positive	Negative	Negative, had erythema nodosum
21	Negative	Positive	Negative	First infection foci
8	Negative	Positive	Negative	First infection foci with pleural effusion
10	Negative	Positive	Negative	Pleural effusion only
25	Negative	Positive	Negative	Reinfection pulmonary tuberculosis
15	Positive		Negative	Reinfection pulmonary tuberculosis
4	No record	Positive	Negative	Reinfection pulmonary tuberculosis
85				

CONCLUSIONS

Young adults who have not been previously infected with tubercle bacilli become contaminated in large numbers during their course of training in some schools of nursing and medicine.

A positive reaction to tuberculin in a person who has previously shown no reaction to the test is the first obtainable evidence of the presence of tubercle formation in the body.

A few weeks is usually required after tubercle formation begins before the tissues are sufficiently sensitized to tuberculo-protein to react positively to tuberculin.

At the time the reaction to the tuberculin test first becomes positive there usually is no external manifestation of tuberculosis. Symptoms are absent, there are no abnormal physical signs and roentgenograms rarely bring to light the location of the disease.

In a small percentage of those who in adult life become contaminated for the first time the focus of the disease when located in the pulmonary parenchyma attains sufficient size to cast a shadow on the x-ray film which can be visualized by the naked eye. Such shadows usually become visible during the first three or four months after the

infection has occurred. When these shadows reach their maximum size, they may show the same general appearance over a period of many months, after which they gradually recede. In some cases the shadows remain, revealing evidence of fibrous and calcium deposits, while in others they completely disappear.

The first infection type of tuberculosis as observed in our group of adults has resulted in no significant symptoms or abnormal physical signs throughout the entire course of development. Indeed, the lesions in the majority of our cases would not have been known to exist had it not been for periodic tuberculin testing and the making of roentgenograms of the positive reactors.

In our experience adults in whom the first infection type of tuberculosis develops, even with considerable involvement of the pulmonary parenchyma and regional lymph nodes, do not require treatment in any form.

The prevention of tuberculosis of the first infection type among young adults consists of protecting them against exposure to patients with communicable tuberculosis. For students of nursing and medicine this amounts to a strict technic for dealing with contagious diseases.

Apparently it makes little or no difference at what time of life the first infection with tubercle bacilli occurs, with reference to the evolution of tuberculosis in the human body. When the first infection type of disease occurs in the second and third decades of life it is just as benign as when it occurs in childhood.

Among those persons in whom through exposure to patients with communicable tuberculosis the first infection type of disease develops, whether in infancy, childhood or adult life, including the third decade, a considerable number will subsequently show a reinfection clinical form of tuberculosis.

Tuberculous pleurisy with effusion as it appeared in our group has been regarded as a reinfection form of tuberculosis. It has occurred only among those persons whose tissues were sensitized to tuberculo-protein. In some of our cases the first infection focus in the lung was not located by roentgen examination, while in others it cast shadows definitely visible on the film, and in such cases the shadow usually preceded the appearance of the effusion.

During our period of observation we have seen the complete evolution of tuberculosis and have observed practically every step in its development, from the time before the tissues became sensitized to tuberculo-protein until death occurred from consumption.

There is usually a period of many months or even years between the development of the first infection type of tuberculosis and the appearance of the reinfection type of disease.

In those subjects who became sensitized to tuberculo-protein under our observation and in whom clinical pulmonary tuberculosis later developed, we were unable to see any difference in the intensity of the disease or in the response to treatment from that in a group of young adults in whom reinfection forms of tuberculosis had developed but who were known to have been infected in infancy or childhood.

By roentgen examination alone it is impossible to differentiate between the first infection and the reinfection type of tuberculosis during the earlier periods of development. Neither produces symptoms or abnormal physical signs. Therefore, a long period of observation is entailed. If the lesion proves to be of the first infection type, symptoms and physical signs do not appear, and the shadow gradually recedes. If it is of the reinfection type, symptoms may appear later, abnormal physical signs may be elicited and the shadow on the roentgenogram may increase in size or show evidence of cavity formation or both.

The tuberculin test should be administered to the negative reactors in schools of nursing and medicine at least every six months, since an interval of a year or more between tests materially reduces the value of a positive reaction in differentiating between the first infection and the reinfection type of disease roentgenographically.

The lesions which developed in our group of adults who showed a positive reaction to the tuberculin test when our observations began were similar to the reinfection types of lesions which developed among students after we had seen the benign first infection type of disease develop.

The fact that a roentgenogram of the chest shows no evidence of disease in a subject in the teens or early twenties is no indication that } pulmonary tuberculosis will never develop. It is our opinion that this disease may develop in any decade of life from endogenous reinfections or exogenous first infections or reinfections.

The cases of tuberculosis reported in this paper for the most part are from a student body of approximately 12,000. In this student body the number of students enrolled in the schools of nursing and medicine is a relatively small group, yet there is an overwhelming preponderance of lesions in this minor group, indicating to us that the problem of tuberculosis among young adults is most acute among those students who while in the line of duty come in contact with tuberculous patients.

HIGH ALTITUDE DISEASE

CARLOS MONGE, M D

LIMA, PERU

Much has been written on the disturbances produced by high altitudes, but Prof Monge was the first to establish the existence of definite clinical entities produced by maladaptation to life at a high altitude, studies which were first published in 1928 in a monograph entitled "La enfermedad de los Andes" Prof Monge has written, at my request, a summary of the disease which justly bears his name—Monge's disease, and it has been my privilege to act as translator

—E S Guzman Barron, Chicago

A man who is acclimated to the high plateaux of the Andes (from 10,000 to 16,000 feet, 3,000 to 5,000 meters, above sea-level) is, *sensu strictiori*, one who by ancestral or acquired changes has the racial characteristics which allow him to behave physically and mentally like a man living at sea-level. Thus it has been shown by many investigators that dwellers at a high altitude differ from those at sea-level both from an anthropologic and from a biologic point of view. Among the differences have been noted erythremia, an increased viscosity of the blood, a diminished oxygen saturation of the arterial blood, an increased vital capacity and a diminished carbon dioxide tension of the arterial blood.¹

Acclimation to a high altitude may be congenital or acquired. The first type defines itself. The second type requires a readjustment of the biologic mechanisms for fitness to life at a high altitude. It is interesting in this connection to recall Father Calancha's² observations, published in 1639, that the Spanish conquerors who went to the mines of Potosí, Bolivia, at an altitude of 14,000 feet (4,300 meters) had no offspring until fifty-eight years after the city was founded. The mechanisms which enabled the Spaniards to become adapted were established slowly indeed.

It is a matter of common experience that many persons living at high altitudes, whether natives or not, have either lost or failed to acquire the necessary adjustments for a normal life in these regions. The acute form of maladaptation, mountain sickness, has been described

From the Medical Clinic, the Faculty of Medicine

1 Monge, M C. La enfermedad de los Andes, Lima, Facultad de Medicina de Lima, 1928. Les erithremies de l'altitude, Paris, Masson & Cie, 1929, *Climatophysiology et climatopathologie des haux plateaux*, in *Fraite de climatologie biologique et medicale*, Paris, Masson & Cie, 1934.

2 de la Calancha, Antonio. Cronica moralizada de la orden de San Augustin, Barcelona, Imp. Pedro Lacaballeria, 1639, vol. 1.

many times, and its symptoms need not be discussed here. Of interest, however, are the bodily disturbances produced by the prolonged effects of a high altitude on those unadapted subjects, clinical entities which my colleagues and I observed among the residents of the Peruvian Andes in the course of our studies of the pathologic conditions due to high altitudes and which have been described under the name Andes diseases.

The clinical picture of high altitude disease may present a variety of forms, the predominance of a particular symptom depending on the degree of damage produced in the different organs and tissues by prolonged anoxemia. It has nevertheless been possible to observe the predominance of two types of this disease: (1) an erythremic type, which we have designated *high altitude erythremia*, on account of the resemblance of the symptoms to those of the Osler-Vaquez erythremia, and (2) an emphysematous type, in which the respiratory symptoms are more important. Also we have observed numerous patients with cardiac, renal and digestive disorders caused by prolonged anoxemia due to living at a high altitude.

HIGH ALTITUDE ERYTHREMIA

This type of high altitude disease has been the one most frequently observed by us. It may take one of two forms: a mild, *subacute mountain sickness*, or a severe, *chronic mountain sickness*.

Subacute Mountain Sickness—The symptoms of this form of mountain sickness appear insidiously and are characterized by a slight diminution in mental and physical fitness. The patient complains of general fatigue which bears no relation to the work he performs. It is in these cases that the characteristic erythremic color of the dweller at a high altitude is seen. The patient becomes cyanotic when he makes the least effort. Cephalalgia sometimes appears after a brief mental effort has been made, there is a tendency to sleepiness, which is easily interrupted by a sensation of asphyxia, which disappears after voluntary breathing occurs. More frequently respiration is of the periodic type. There is marked congestion of the mucous membranes (ocular, nasal and oral), and epistaxis, aphonia and ostalgia are marked (the Indian word *macolca* designates this symptom). Digestion is slow, and constipation appears. Loss of weight is generally noted. The patient with the more benign form, if he came originally from sea-level, thinks himself acclimated and goes on with his daily work, to find later that he is unable to keep up the kind of life to which he was accustomed at sea-level. If the disease continues nausea appears, sometimes with vomiting, dizziness and a diminution of the visual acuity, which is

characterized by difficulty of continuous reading and is expressed by the patient as "cloudiness" of vision. Varied paresthesias, such as paracusia, occur. Sometimes these symptoms subside. In some cases the patient goes back to a city at sea-level to consult a physician and finds with surprise that all his symptoms have disappeared. He is sent home by the doctor, who says that the condition is due to nervousness, but once the patient is back at the high altitude the symptoms reappear. This form of the disease permits the patient to live for a long time. The number of red blood cells in such a patient is about 7,000,000 per cubic millimeter. The number of leukocytes is sometimes slightly



Fig. 1—A native of Peru with high altitude disease

increased, and there is a slight increase in the number of monocytes. We have at times observed a few macrophages in the peripheral blood, their presence having no relation to the severity of the disease. The hemoglobin in the blood is increased from 10 to 20 per cent. The p_H of the blood (colorimetric) in the five cases in which it was measured was 7.48. (For twenty-two normal subjects in Oroya, Peru, at 12,200 feet [3,650 meters] we found an average of 7.45.) The basal metabolic rate, studied in collaboration with Hurtado,³ was found to be normal in seven of ten cases, in the other three it was below normal (—31, —27 and —16, respectively). The disappearance of the disease means

³ Hurtado, A. *Am J Phys Anthropol* **17** 137, 1932

complete acclimation to life at a high altitude. Otherwise, severe and important symptoms may appear, such as those grouped under the name chronic mountain sickness.

The Severe Form of High Altitude Erythremia, or Chronic Mountain Sickness—In this form of the disease the resting patient becomes florid and turns purple at the least effort, the erythremic aspect is more striking in natives because of their dark color. In a white patient the skin appears blue. This characteristic color is more noticeable in the face, ears, nose and hands, the dark cyanotic color being more conspicuous when compared with the brownness or whiteness of the body. In cases of severe involvement the scleras are intensely colored by the distended capillaries, the eyes being hidden behind edematous and bluish

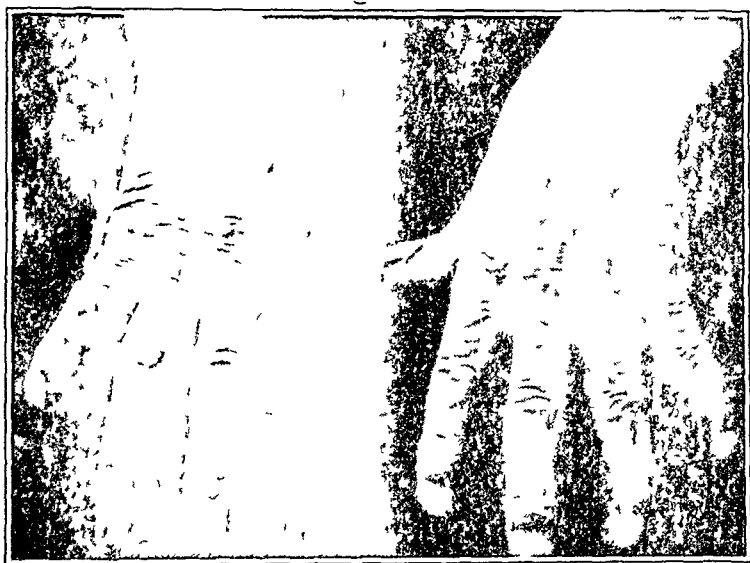


Fig. 2—The characteristic appearance of the hands of a patient with high altitude disease

eyelids, the face is blue-violet, almost black, resembling that of an asphyxiated person, the nasal and oral mucosae are wine red, epistaxis is frequent, aphonia is usually noted, and the tongue appears larger than normal and full of blood, with prominent papillae. The skin of the body is dry, while the forehead and hands are covered with sweat, even in cold weather. The hands become enlarged and turgid, accompanied with considerable distention of the superficial veins and clubbing of the fingers. The nails become thick, opaque and vertically striated and appear to be inserted like watch glasses. The thorax is large and of an emphysematous type. Walking is slow, the patient being obliged to stop frequently. He resembles an old emphysematous, plethoric patient, walking slowly and heavily. He feels extremely weak, has a marked tendency to sleep and not infrequently is found in a state of

drowsiness, indifferent to what happens outside, with no desires, even to take food. When awakened from this lethargic state he complains of general malaise and a sensation of anguish, spells of dizziness and fainting commonly occurring. Blurring of the vision, nausea and vomiting at the least effort are noted. Sometimes the patient suddenly falls into a coma for two or three hours, to return later to his pitiful condition.

Digestive System.—In general it is an inability to take food rather than anorexia that makes eating difficult, for the discomfort increases considerably after the ingestion of food, and signs of asphyxia frequently come with swallowing. Vomiting is frequent. On occasions there are crises of diarrhea.

Respiratory System.—The patient lives in a state of insufficient hematosi and has incessant dyspnea. The vital capacity diminishes progressively. Aphonia, coughing and frequently bronchitis are present. Sometimes there are also recurring congestive processes in the lungs accompanied with hemoptysis, with or without fever, all of which symptoms rapidly disappear when the patient goes down to sea-level.

Circulatory System.—In the majority of cases cardiac disorders are not found for a long time. We have frequently observed a doubling of the second tone. With the progress of the disease comes cardiac insufficiency. In one case symptoms of angina pectoris appeared after exertion but later disappeared when the patient descended to a low altitude. In this particular case, when the patient tried to keep on walking his vision grew cloudy, he would then become unconscious and fall suddenly. There are no constant alterations in the arterial blood pressure, rarely hypertension occurs. Sometimes a patient is seen who has cardiac insufficiency due to anoxemia without erythremia, the symptoms disappearing as soon as he is brought down from the high altitude. There is generalized dilatation of the blood vessels of the skin and mucosae, which is an exaggeration of a phenomenon normal at high altitudes and which, combined with a plethora of blood, is the cause of numerous disorders. The plethora is responsible also for the considerable loss of blood in case a wound is sustained.

Special Senses.—We have observed a variety of disorders of the sense organs which may be ascribed to dilatation of the capillaries, such as cloudiness of vision, temporary blindness, in which Dammert observed considerable dilatation of the capillaries of the retina, and temporary deafness, in which Raffo observed generalized vasodilatation of the tympanic membrane.

Liver and Spleen.—In only two of seventeen cases in which there was no cardiac insufficiency was the size of the spleen moderately increased. In two cases there was hypertrophy of the liver.

Nervous System—Patients with this disease complain of a variety of algeias and paresthesias. Some complain of excruciating pain in the lower extremities, with no history of syphilis and a negative Wassermann reaction, others have constant pain in the lumbar region or in the joints, pain of such intensity that they are obliged to remain in bed for several days at a time. This pain may disappear spontaneously. In one case the pain disappeared as the patient descended by train from an altitude of 14,800 feet (4,500 meters) to sea-level in twelve hours. There is sometimes violent cephalalgia. In one instance the cephalalgia subsided after lumbar puncture was performed. Bleeding immediately improves the condition in such cases and is used frequently by the Indians. Paresthesias are varied in type and localization. Some patients complain of unpleasant sensations of heat in the face, others, of violent sensations of cold. One patient said he felt as if warm water were being thrown on his back, another complained of closely localized sensations of pain in the hands and feet. One had the sensation of the loss of one hand, another complained of "bandaged legs." The patients whom we studied while they were at high altitudes unfortunately had had imperfect neurologic examinations, and when they reached sea-level we were unable to find any signs of importance.

Mental Disturbances—In cases of severe involvement it is possible to find marked disturbances in the behavior and memory of the patients, the entire psychic personality appearing altered. One of our patients, an engineer, had crises of mental confusion during which he would make gross mistakes in arithmetic and drawing, mistakes which he corrected once the crisis was over. As the disease advances the patient becomes apathetic and indifferent to his environment, nothing interests him, and even with the knowledge that descending to sea-level will effect a cure, he does not take the initiative in making the trip. One of our patients who felt ill and tired at a high altitude refused to go down to sea-level when advised to do so. He was taken down while in a coma, which disappeared as soon as he reached sea-level. It should be mentioned that similar observations have been made by Barcroft in his studies with pneumatic chambers.⁴

Blood—Marked polycythemia is the characteristic feature in these patients, the number of red blood cells being as a rule around 7,000,000, i. e., higher than the average count at those altitudes, which is about 6,000,000. In one case we found a count of 9,060,000 erythrocytes. The number of reticulocytes also is increased. There is slight leukocytosis in most cases, although in one instance we found only 4,000 leukocytes. There is a predominance of monocytes, and in some cases we noted

4 Barcroft, J. J. Physiol. **42** 63, 1911

macrophages and cells of the histiocytic type. We were not able to study the platelets. Alterations in the process of clotting are manifest. One patient had bleeding of the gums when he lived at an altitude of 14,800 feet (4,500 meters), but this disappeared as he went down to a level of 14,000 feet (3,700 meters). In another case the patient had convulsive attacks accompanied with purpura and the presence of blood in the cerebrospinal fluid, all of which disappeared when he was brought down to sea-level. Epistaxis is frequent. In general the bilirubin content of the blood is increased (1.28 mg per hundred milligrams in one case and 1.62 mg in another). The van den Bergh reaction is of the indirect type. The p_H of the serum, like that of a normal subject living at a high altitude, is slightly more alkaline than when he is at sea-level. In one case of coma the p_H of the serum was found to be 7.35, while after the crisis had passed it went up to 7.45. The alkaline reserve of the plasma is greater than that of a person who is acclimated to a high altitude. When a patient is brought to sea-level no perceptible alteration in the acid-base equilibrium is noted, as the composition of the blood returns to normal quickly. Determinations of the protein content of the blood have not given concordant figures. In one case there was a diminution of about 50 per cent, in other cases normal values were obtained. The concentration of hemoglobin in the blood is considerably increased, in one case reaching 179 per cent (taking 100 as the value found at sea-level). In this particular case 90 per cent of the blood volume was made up of erythrocytes, as determined with the hematocrit. As a consequence of the increased concentration of hemoglobin, the viscosity of the blood is increased. The oxygen saturation of the arterial blood is decreased. Hurtado found in one of our patients a saturation of 57 per cent. Although we have not yet studied systematically the relationship of the oxygen saturation of the arterial blood, the utilization of oxygen and the severity of the symptoms in this disease, we give in table 1 the oxygen utilization (studied in Oroya, Peru) in one adapted subject and two patients. We may say that all these chemical studies were only of a preliminary nature and that well coordinated biochemical studies are of prime necessity in determining the exact nature of the disease.

Basal Metabolism—While the basal metabolism of normal persons living at a high altitude is normal, according to Hurtado,³ in ten persons who presented the symptoms of mild erythremia we obtained the following figures: —1, —14, —3, —4, 0, —31, —9, —27, —6, —36 and —12. It seems that in these mild forms of the disease there is a diminution of the basal metabolism which approaches and reaches normal values with acclimation. In table 2 are given the data obtained by Hurtado for six of our patients who were suffering from severe erythremia. The

difficulty of making studies of the gas exchange in untrained, ignorant persons prompts us to be cautious about our investigations in this subject

Genito-Urinary System—The patients frequently complain of sexual frigidity. We have seen patients with albuminuria which disappeared when they were brought to sea-level but which returned as soon as they went back to the high altitude. One patient, who lived at an elevation

TABLE 1—*Data on the Utilization of Oxygen by the Tissues of Normal and Erythremic (Due to High Altitude) Subjects at a High Altitude*

	Normal Subject		Erythremic Subjects	
	At 150 M	At 3,700 M	Severe Erythremia at 3,700 M	Improved at 150 M
Hemoglobin, %	100.0	117.0	178.0	105.0
Arterial blood				
Oxygen saturation, %	96.0	88.0	56.0	81.0
Oxygen tension, mm	110.0	65.0	35.0	52.0
Oxygen in blood, vols %	18.5	21.6	32.9	19.4
Venous blood				
Oxygen saturation, %	58.0	36	45	54
Oxygen tension, mm	37.0	36	31	35
Oxygen utilized, %	38.0	32	11	27

TABLE 2—*Data on the Basal Metabolism Obtained by Huntado for Patients with Severe Erythremia at an Altitude of Three Thousand, Seven Hundred Meters^{*}*

Age	Height, M	Weight, Kg	Surface Area, Sq M	Pulse Rate per Min	Respiration per Min	Basal Metabolic Rate (Aub Du Bois), %
60	1.56	51.9	1.50	78	12	+67
47	1.60	56.6	1.59	84	12	+20
31	1.67	75.4	1.85	75	16	+23
76	1.63	73.4	1.80	55	18	+18
29	1.65	59.0	1.65	60	16	+15
33	1.53	57.7	1.56	48	18	+30

* The barometric pressure was 480 mm of mercury and the temperature from 13 to 18 C (55.5 to 65 F)

of 13,000 feet (4,000 meters), came to sea-level complaining of definite symptoms of renal insufficiency, the symptoms subsided and disappeared while he was at sea-level.

Evolution of the Disease—As a rule, the patients consult a physician only after the illness has been present for some time, for from two to twenty years in about one hundred patients seen by us. Sometimes a patient becomes temporarily well even while staying at a high altitude. As a rule, after a stay at sea-level a patient can return to a high altitude and live there for some time without great discomfort. As time goes on, however, the cure at sea-level is less and less enduring, and asphyxial

disorders may occur as soon as the patient reaches a high altitude, disorders which sometimes end in death. Yet even in cases of severe involvement accompanied with anoxemic coma, a descent to sea-level brings general improvement. If the patient stays at a high altitude death may result from hemorrhage, pulmonary thrombosis, bronchopneumonia or progressive cardiac insufficiency.

We must point out the great similarity between the erythremic type of this disease and the essential erythremia first described by Vaquez, the difference being that erythremia due to a high altitude subsides immediately when the patient descends to sea-level.

EMPHYSEMATOUS TYPE

The emphysematous patient always has a long history of frequent bronchitis and laryngitis. The dominant symptom is dyspnea, which develops after the least effort. Cyanosis occurs rapidly. It is not uncommon to see repeated attacks of congestion of the lungs accompanied with hemoptysis. The thorax is globular, with increased resonance to percussion, the vital capacity is considerably diminished. The fingers are clubbed. The insufficiency of the right side of the heart appears rapidly. The pulmonary ventilation is diminished, and as a consequence the alkaline reserve and the alveolar carbon dioxide content are relatively increased. We may say that the condition resembles that described by the Argentine clinicians as Ayerza's disease.⁵ Hurtado, who has studied this type particularly,⁶ found a low oxygen saturation in the arterial blood (ranging from 72 and 65 to 55 per cent). In one case he found a high carbon dioxide content in the arterial blood. In those cases in which there is accompanying acidosis, the symptoms disappear slowly, even when the patient is brought to sea-level.

From this condensed description it is seen that the fundamental characteristic of high altitude disease, the characteristic which has made us group it as a nosographic entity, is the fact that all the symptoms subside or disappear as soon as the patient is brought down to sea-level. This feature is undoubtedly due to a common cause, anoxemia. The predominance of any one symptom must be due to the fact that the particular organ involved has suffered the most damage from the prolonged effects of oxygen want.

5 Escudero, P. *Enfermedad de Ayerza*. La enfermedad de Ayerza y los cardiacos negros, in *Publicaciones de la Clinica del Profesor P. Escudero*, Buenos Aires, El Ateneo, 1925, vol. 1, p. 19.

6 Hurtado, A. *Sobre la patologia de la altura*, Lima, Minerva, 1930.

BRITTLE BONES AND BLUE SCLERAS IN FIVE GENERATIONS

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The syndrome of brittle bones and blue sclerotics is one of those comparatively rare yet interesting hereditary clinical entities which stir the imagination and excite the curiosity of clinician and investigator alike. It is our purpose here to report a case, including a family history of five generations, and to review briefly some of the recent literature bearing on the subject.

Key¹ in 1926 and Bell² in 1928 presented comprehensive monographs on this subject. The former furnished the first complete pathologic study while the latter investigated particularly the hereditary phase and through an exhaustive study of all reported cases presented the most accurate known statistics as to the incidence. A review of their work should constitute a starting point for any discussion of this subject. To this summary will be added other recent contributions.

HISTORY

According to Bell,² fragility of the bones due to cancer, tuberculosis and syphilis was described by Marcellus Donatus (1588), Fabricius (1609) and Fontanus (1639). Courtial (1705) noted that the bones of aged persons are as fragile as those of persons who have taken large quantities of mercury. A few years later the suggestion was made that osseous fragility may be inherited, but since the various causes of fragility, such as cancer, osteomalacia and rickets, were not well known, little progress toward an understanding of the hereditary feature of the syndrome was made. In 1788, however, Eckman noted hereditary fragility in three generations, and by the middle of the nineteenth century records of some thirty families had been collected.

1 Key, J. A. Brittle Bones and Blue Sclera. Hereditary Hypoplasia of the Mesenchyme, *Arch Surg* **13** 523 (Oct) 1926.

2 Bell, J. Blue Sclerotics and Fragility of Bone, in Pearson, K. *Treasury of Human Inheritance*, London, Cambridge University Press, 1928, vol. 2, pt. 3, sect. 24.

which showed a hereditary tendency to fracture. However, no mention of blue sclerotics was made in these reports.

In other connections, however, abnormally blue sclerotics had received passing notice, and von Ammon³ in 1841 demonstrated by means of pathologic dissections that the effect is due to the fact that the choroid coat shines through an abnormally thin sclerotic coat. Credit for the first mention of the association of blue sclerotics and fragile bones goes to Spurway⁴. In 1896 he reported the occurrence of hereditary osseous fragility in four generations and remarked on the "curious bluish tinge of the eye-ball" common to many members of this family." Four years later Eddowes⁵ wrote his classic paper pointing out the association of osseous fragility and blue sclerotics. He reported on four generations of a family and showed not only that the peculiar syndrome was inherited but that it followed the mendelian law, appearing as a dominant character.

In 1917 Bronson⁶ and van der Hoeve and de Kleijn⁷ independently brought forth the striking observations that persons with this syndrome tend in the third and fourth decades to become deaf. This deafness was later found to be due to otosclerosis. Thus the triad brittle bones, blue sclerotics and deafness was finally established. Later a fourth feature was to be added, namely, relaxation of the ligaments.

NOMENCLATURE

Great confusion has existed in the past and continues to exist in the contemporary literature with reference to the classification of brittle and soft bones. Such a situation is easily understandable when it is considered that in many instances of abnormality of the bones there is no known etiology, and in some cases there is failure to represent even a recognized syndrome. The following terms are encountered, many of which are synonymous: osteogenesis imperfecta, periosteal dysplasia, mollities ossium, osteomalacia, fetal rickets, fragilitas ossium, osteoporosis and osteopsathyrosis. On the other hand, there is a group of well known diseases which produce a variety of osseous lesions. We

3 von Ammon, F. A. Klinische Darstellungen der angeborenen Krankheiten und Bildungsfehler des menschlichen Auges, Berlin, G. Reimer, 1841, p. 73.

4 Spurway, J. Hereditary Tendency to Fracture, Brit. M. J. **2**: 845, 1896.

5 Eddowes, A. Dark Sclerotics and Fragilitas Ossium, Brit. M. J. **2**: 222, 1900.

6 Bronson, E. Fragilitas Ossium, Edinburgh M. J. **18**: 240 (April) 1917.

7 van der Hoeve, J., and de Kleijn, A. Blue Sclera, Fragile Bones and Deafness, Arch. f. Ophth. **95**: 81 (Jan.) 1918.

are not concerned here with this group, though it may be pointed out that rickets, scurvy, syphilis, metastatic carcinoma, multiple myeloma, osteogenic tumors, bone cysts and hyperparathyroidism can produce changes which make bones either soft or fragile. Descriptive terms derived from these diseases are frequently applied to osseous lesions. The greatest confusion, however, is seen to lie in the group of idiopathic or developmental osseous changes. Probably the best classification for the different types of idiopathic fragility is a modification of that given by Babcock⁸

I Hereditary type

- 1 Hereditary hypoplasia of the mesenchyme (brittle bones and blue scleras)

II Nonhereditary congenital type

- 1 Osteogenesis imperfecta congenita
- 2 Osteogenesis imperfecta tarda (osteopsathyriosis)
 - (1) With white scleras
 - (2) With blue scleras

III Nonhereditary acquired type

- 1 Osteosclerosis fragilis generalisata (marble bones, or Albers-Schonberg's disease)

IV Senile type

- 1 Osteoporosis

Osteogenesis imperfecta was first described by Lobstein⁹ in 1833. Many observers now believe that the pathologic process is essentially the same in the two types of osteogenesis imperfecta, the term congenital being reserved for multiple fractures present at birth while the term late refers to fragility developing after the second year of life.

Key¹ separated osteogenesis imperfecta entirely from fragility of the bones in persons having definite antecedents with the condition. The hereditary osseous fragility associated with blue scleras he designated hereditary hypoplasia of the mesenchyme. It is with the latter condition that this paper is primarily concerned.

⁸ Babcock, W. W. A Text-Book of Surgery, Philadelphia, W. B. Saunders Company, 1935, p. 203.

⁹ Lobstein, J. G. C. F. M. Traité d'anatomie pathologique, Paris, F. G. Levrault, 1833, vol. 2, p. 204.

HEREDITY

With few exceptions the disease is remarkably hereditary. Isolated cases have been recorded, however, such as those reported by Bowcock and Lewis,¹⁰ Goin,¹¹ Loddon,¹² and Dessoff,¹³ in which no hereditary influence could be elicited. Bell¹⁴ pointed out that females are especially liable to the condition, constituting 55 per cent of the patients whose cases have been reported. As is the case in night blindness, dichromatism, hemophilia and hereditary atrophy of the optic nerve, females are the more potent transmitters of this anomaly. Furthermore, the disease as represented by its most typical defect, the blue sclerotics, is a true mendelian dominant character. One would expect that 50 per cent of the offspring of a heterozygotic person with this condition mated with a normal person would have blue sclerotics and brittle bones. This, indeed, has proved to be the case in the many series already studied. With the aforementioned exceptions, one may conclude that each affected person has an affected parent and that the affected person, in turn, will have an equal number of affected and unaffected children. The unaffected children will not have affected descendants. A generation is never skipped, as is occasionally the case with hemophilia ("knight's move" of Bateson). Since the deafness occurs rather late in life, its presence is less often recorded in statistics. But just as blue scleras and fragile bones are a part of the syndrome, so also is otosclerosis, and therefore, though appearing late, it conforms to the hereditary rules just enumerated. Bell¹⁵ has contributed a most complete hereditary study of this syndrome.

Recently, interesting cases with a record of the antecedents have been published by Møller,¹⁶ Stevenson and Cuthbertson,¹⁷ Kersley,¹⁸ Holcomb,¹⁹ Constans,²⁰ Mucklow,²¹ Levent,²² Hilgenfeldt,²³ and others.

10 Bowcock, H. M., and Lewis, G. T. Brittle Bones and Blue Sclera. Report of a Case with Glycosuria, *Ann Int Med* **3** 700 (Jan) 1930.

11 Goin, L. S. Idiopathic Osteopsathyrosis, *Am J Cancer* **17** 668 (March) 1933.

12 Loddon, G. A Case of Blue Sclera (Osteopsathyrosis). *Boll d'ocul* **11** 65 (Jan) 1932.

13 Dessoff, J. Blue Sclerotics, Fragile Bones and Deafness, *Arch Ophth* **12** 60 (July) 1934.

14 Bell, J. A New Pedigree of Human Inheritance, *Ann Eugenics* **4** 41 (April) 1929.

15 Bell^{2, 14}

16 Møller, E. Family Tree of a Patient with Eddowes' Syndrome, *Acta med Scandinav* **69** 223, 1928.

17 Stevenson, G. H., and Cuthbertson, D. P. Blue Sclerotics and Associated Defects, *Lancet* **2** 782 (Oct 10) 1931.

GENERAL PHYSICAL CHARACTERISTICS

Apart from the specific physical defects already enumerated, it has been repeatedly observed that such persons tend to be undersized. They are short and slender and many times refer to themselves as being "small boned." The normal contours are occasionally altered by the development of bony deformities. The literature carries many illustrations of extreme instances in which the limbs and spine are warped into bizarre shapes as a result of many fractures. In addition to these deformities, frequently there is anomalous cranial ossification tending to produce protuberances in various regions. These may be bitemporal, occipital or frontal. Apert, Bach and Odinet²⁴ described a patient who showed "a voluminous cranium" and "an osseous bump projecting above the ears." The temporoparietal and sagittal sutures have been reported by Brinson⁶ as gaping. Arlabosse²⁵ also reported a case in which there were cranial deformities. Joachim and Wasch²⁶ studied three patients exhaustively and noticed in all a prominence of the veins, indicating phlebosclerosis. As far as we are aware, that was the first time such an observation had been made. Apart from the abnormal characteristics noted, however, these persons appeared to enjoy good general health and showed the same intelligence as that of their normal brothers and sisters.

BLUENESS OF THE SCLERAS

The blue sclerotics stand out as the most striking feature. As one looks at an affected person, one is struck by the china-blue color of the sclerotics, and as the majority of these subjects exhibit a rather

18 Kersley, G. D. Brittle Bones, Blue Sclerae and Deafness, *St. Barth. Hosp. J.* **38** 236 (Sept.) 1931.

19 Holcomb, D. Y. Fragile Boned Family. Hereditary Fragilitas Ossium, *J. Hered.* **22**:105 (April) 1931.

20 Constans, G. M. Blue Sclera and Brittle Bones. *Journal-Lancet* **49** 507 (Nov. 15) 1929.

21 Mucklow, S. L. Osteogenesis Imperfecta Tarda (Idiopathic Fragilitas Ossium). Two Cases, *Brit. J. Radiol.* **6** 294 (May) 1933.

22 Levent, R. Lobstein Syndrome Compared with van der Hoeve Syndrome, *Gaz. d. hôp.* **105** 1901 (Dec. 21) 1932.

23 Hilgenfeldt, O. Contribution to the Disease Picture of Idiopathic Abnormal Bone Fragility, *Deutsche Ztschr. f. Chir.* **238** 433, 1933.

24 Apert, E., Bach, E., and Odinet. Presentation of a Family Affected with Osteopsathyrosis and with Blue Sclerae, *Bull. Soc. de pédiat. de Paris* **26** 21 (Jan.) 1928.

25 Arlabosse, J. A Case of Fragilitas Ossium with Head Deformities and Blue Sclerotics, *J. de radiol. et d'électrol.* **15** 92 (Feb.) 1931.

26 Joachim, H., and Wasch, M. G. Fragilitas Ossium in Five Generations, *Ann. Int. Med.* **7** 853 (Jan.) 1934.

delicate or even dainty appearance along with the bluish eyes, they have been said to look doll-like. Most students have agreed with the early conclusions of von Ammon³ that the blue is imparted by the choroid and is more apparent than usual because the sclera is thin and therefore more transparent. Possibly "thin sclerotic" would be a term preferable to the misnomer "blue sclerotic." To substantiate this theory, Bell² pointed out that ophthalmologists who have operated on such eyes and who have examined them with the slit lamp believe that the sclera is thin. However, Bronson⁶ and later Patterson, quoted by Oast,²⁷ found the sclera to be of normal thickness. An increased translucency rather than a decreased thickness has been suggested as a cause. Friedberg²⁸ more recently has found a decrease in the content of lime salts, which he said he believed accounted for the increased transparency. Levander²⁹ observed an even darker shade near the iris, indicating various degrees of transparency in the sclera.

Fortunately in these persons there does not appear to be an increased liability for other ocular lesions to be associated with this alteration in the fibrous tunic. Visual defects, refractive errors and variations from the normal ocular tension have not been noted to occur more frequently. One is again struck by the sharp differentiation of tissue, not only quantitative but qualitative, which this disease presents.

DEAFNESS

That deafness occurs in this syndrome was first observed by Adair-Dighton³⁰ in 1912. But full credit must be given to van der Hoeve and de Kleijn,⁷ who, simultaneously with Bronson,⁶ in 1917, showed that a hereditary type of deafness is really an integral part of the syndrome. This feature most frequently becomes manifest after the subject is 20 years old and is said to be of the type ascribed to otosclerosis. The deafness in otosclerosis is due to a process resembling osteitis fibrosa, occurring in the otic capsule, which on subsiding heals, with the formation of "scar bone" that causes complete ankylosis of the stapediovestibular articulation, thus precluding the transmission of sound waves to the internal ear. There are few reports in the literature of the pathologic study of the ears in these cases. As with most forms of conduction deafness, however, hearing for all air-conducted sounds,

27 Oast, S. P. Blue Sclerotics and Brittle Bones. Report of Occurrence in Mother and Child, *Arch. Ophth.* **57** 254 (May) 1928.

28 Friedberg, C. K. The Nature and Existence of Abnormal Fragility of Bone, Blue Sclera and Impaired Hearing, *Klin. Wchnschr.* **10** 830 (May 2) 1931.

29 Levander, G. A Case of Brittle Bones and Blue Sclera, *Acta chir. Scandinav.* **63** 301, 1928.

30 Adair-Dighton, C. A. Four Generations of Blue Sclerotics, *Ophthalmoscope* **10** 188, 1912.

from the lowest through the highest, is impaired, while bone conduction remains practically normal

Friedberg²⁸ pointed out that both nerve and conductive types of deafness occur in patients with this syndrome, and he uses this as a strong argument against hereditary hypoplasia of the mesenchyme. He said he believed the syndrome to be due to a defect in the organ and not to a defect in the primitive germ layer. In the family which we studied there was a history of deafness in fifteen of twenty-seven affected members, or 55 per cent. Aside from the fact that the mother of our patient had the otosclerotic type of deafness, we have no means of knowing which type was present in our family. Van der Hoeve and de Kleijn⁷ reported cases in which the petrous portion of the temporal bone was opaque to roentgen rays, and they stated that this fact may be an aid in diagnosis because it shows abnormal calcification of the otic capsule. Kompanejetz³¹ has described rather extensively the causes of deafness in this disease. Strange combinations, such as those reported by Lannois and Gaillard,³² occasionally appear. Their patients were totally deaf sisters, one with and one without blue scleras. The blueness was not noted until adult years, and both patients had associated syphilis, making the relation with this syndrome questionable.

FRACTURES DEFORMITIES AND SPRAINS

To estimate exactly the degree of fragility of bone is difficult. Normal persons have fractures with a fairly constant degree of trauma. The occurrence, however, of two or more fractures in a person with blue sclerotics in contrast to one or no fractures in another member of the same family who has white sclerotics is taken as an indication of fragility. Levander²⁹ has pointed out that the metaphysis becomes thinner just before it reaches the epiphysial line. Many observers have noted that fractures frequently occur at this site. In contrast to osteogenesis imperfecta, the fractures are not likely to be present at birth but do occur off and on through childhood until puberty is reached. After puberty the bones are less likely to break, and the subject may begin to look forward to a more peaceful and less hazardous existence. Comminuted and compound fractures are rare, though our own patient presents an example of the latter condition. Nonunion is seldom encountered, for as a rule the fracture heals promptly without deformity and without excessive callus. Deformity is due to malunion, not to softening of the bones, and for this reason should usually be pre-

31 Kompanejetz, S. Case of Deafness with Blue Sclera and Brittle Bones, *Monatschr f Ohrenh* **64** 193 (Feb) 1930

32 Lannois, M., and Gaillard, R. Blue Sclera and Total Deafness, Acquired and Incomplete, *Ann d'oto-laryng*, February 1933, p. 141

ventable It has been repeatedly emphasized that the bones are unusually hard though brittle Conditions characterized by reabsorption of calcium, on the other hand, may well exhibit softening and its attendant bizarre deformities

The fibrous structures supporting the joints are frequently loose and relaxed, allowing for an unusual range of motion Many such persons are "double jointed" It is not surprising, therefore, to encounter many instances of sprains and dislocations Our patient sustained a dislocation of the hip during a simple fall to the pavement Sprains are said to be more common than dislocations, though the tendency to either is likely to be a prominent feature in only an occasional family

The roentgenographic appearance of the bones is characteristic, in that the density of the entire bone is decreased As a rule the cortex is thin, and there is a wide marrow cavity In contrast to such a diaphysis, however, the epiphyses show a more nearly normal size Occasionally an excessive amount of calcification has been noted in the petrous portion of the temporal bone—presumably in the vestibular region

ETIOLOGY AND PATHOLOGY

Most authorities agree that there is some hereditary defect, but its exact nature has never been determined Key and others have proposed the theory of hereditary hypoplasia of the mesenchyme, and this seems to be the most satisfactory explanation However, it has been pointed out that many other tissues of mesenchymal origin are not affected and that abnormalities have been noted also in ectodermal and entodermal tissues

The etiology has been sought by students of the disease among the endocrine glands, and at one time or another every gland has been suspected Kraus³³ has discussed this thoroughly Fonseca³⁴ has reported two cases in which he said he believed that the condition was associated with a derangement of calcium metabolism and in which parathyroid therapy was followed by improvement For the most part the blood has shown a normal concentration of calcium and phosphorus Dessoiff¹³ has recently made out a case for hyperparathyroidism, and this of all the endocrine disturbances seems the most logical to be considered as a causative factor He cited from the literature two cases of osteogenesis imperfecta associated with enlargement of the parathyroid glands But it must be pointed out that osteogenesis imperfecta, as well as other metabolic diseases of bone attributable to hyperpara-

33 Kraus, E J Relation of Brittle Bones and Blue Sclera to the Endocrine System, *Virchows Arch f path Anat* **274** 37, 1930

34 Fonseca, A The Relation of Parathyroid Function to the Syndrome of Blue Sclerotics, *Brasil-med* **44** 448 (April) 1930

thyroidism, is different from the disease under discussion. Furthermore, with few exceptions, the calcium and phosphorus values for the blood in these cases have been normal.

The pathologic changes in the eyes and ears have already been discussed. Key studied the osseous changes thoroughly and noted especially that there are many wide canals running out through the cortex in all directions and communicating freely. In some of the larger canals collections of fat cells are seen. The bone marrow extends a short distance into the canals, where it is gradually replaced by fat, which is in turn replaced by myxomatous tissue. There is a superabundance of osteoblasts, which accounts for the rapid healing of fractures. The tendons and ligaments are small but are histologically normal.

Brittle teeth have occasionally been noted but are rare. Some members of Stobie's³⁵ family reported breaking a tooth while biting bread. Tanturri³⁶ reported not only brittle teeth but brittle hair and nails as well. None of these features had been noted in our own cases.

DIAGNOSIS, PROGNOSIS AND TREATMENT

A diagnosis of this condition is founded on the presence of abnormally blue scleras in a person one or both of whose parents had the same characteristic. The presence of the other stigmas is not essential to a diagnosis. As a practical matter, however, most patients are first seen because of a fracture, and a diagnosis is made when the blueness of the eyes is noted.

The prognosis will vary with the individual case. It can be predicted that the fractures will unite promptly. Deformities may result from malposition of the fragments but not from bending of the bones. The most encouraging feature is that puberty so often brings about a cessation of the bone breaking, and thereafter fractures are much less likely to occur. No method is known which will prevent the onset of deafness—a tragically important fact in a youth. A person with this defect who marries may anticipate that one half of the offspring will be similarly affected.

Treatment has been empirical and will continue to be so until an etiologic basis is found. Endocrine preparations, drugs, vitamins, diet and physical therapy have all been employed. No method of treatment, however, has been shown conclusively to have any curative effect. Exploration of the parathyroid glands has been proposed but appears

35 Stobie, W. The Association of Blue Sclerotics with Brittle Bones and Progressive Deafness, *Quart J Med* **17** 274 (April) 1924.

36 Tanturri, V. New Factors in the Complex of Blue Sclera, Brittle Bones and Deafness, *Rev españ y am de laring, otol y rin* **23** 97, 1932.

to us illogical for this particular entity. Breuer³⁷ stated the belief that he has seen beneficial results after the administration of strontium lactate and calcium phosphate, $\text{Ca}_3(\text{PO}_4)_2$, the former stimulating the formation of osteoid tissue on which the latter more readily precipitates. Gorter³⁸ has discussed the use of thymus extract. A patient with well controlled osteogenesis imperfecta tarda has recently been shown to be improved in a report by Secord, Wilder and Henderson³⁹. They administered the new thymus extract of Hanson daily for a period of more than three months and were able to demonstrate roentgenographically an improvement in the density of the bones and some thickening of the cortex.

For the present the physician must insist on scrupulous care against injury for the affected child. Fractures when they do occur are treated along accepted lines, the fact being borne in mind, however, that the bones unite quickly and that the period of immobilization may be reduced. Hein⁴⁰ has described in detail methods used in treating an infant who had nine distinct fractures, as noted roentgenographically. Deformities may safely be corrected by osteotomy. The eyes ordinarily require no treatment, while for the otosclerosis, at the present writing, there is little to be done.

REPORT OF A CASE

E. M. C., a white girl aged 10 years, was first admitted to the Union Memorial Hospital on July 3, 1930, having suffered a compound fracture of both bones of the left forearm. Her family history revealed that members of four previous generations on her mother's side had suffered from multiple fractures, had blue sclerotics and in later life had been deaf. The child herself enjoyed good general health. There had been a suspicion of rickets in infancy. A year before her admission to the hospital she fractured a bone in the right forearm, the result, as in this instance, of a minor fall.

The general physical examination revealed no abnormality apart from the injury and from the observation that the child had abnormally blue scleras. There was an irregular laceration 2 cm long on the dorsal surface of the left forearm, and both bones showed marked deformity. Roentgen films confirmed the diagnosis of a fracture of both bones of the forearm in the middle third with

37 Breuer, J. Treatment of Osteogenesis Imperfecta, *Deutsche med Wchnschr* **56** 1735 (Oct 10) 1930.

38 Gorter, E. The Treatment of Fragility of Bones with Thymus Preparations, *Nederl tijdschr v geneesk* **1** 2022 (April 27) 1929.

39 Secord, E. W., Wilder, R. M., and Henderson, M. S. Osteogenesis Imperfecta Tarda (Osteopsathyrosis) Treated with Thymus Extract (Hanson), *Proc Staff Meet, Mayo Clin* **11** 1 (Jan 2) 1936.

40 Hein, B. J. Osteogenesis Imperfecta with Multiple Fractures at Birth. An Investigation with Special Reference to Heredity and Blue Sclera, *J Bone & Joint Surg* **10** 243 (April) 1928.

the fragments displaced (fig 1) Open operation with wiring of the fragments was finally required to obtain a satisfactory result This was carried out on July 8 by Dr P G McLellan, at that time resident surgeon The wound healed satisfactorily, and subsequent observation showed prompt solid union The calcium content of the blood was 98 mg per hundred cubic centimeters, and the

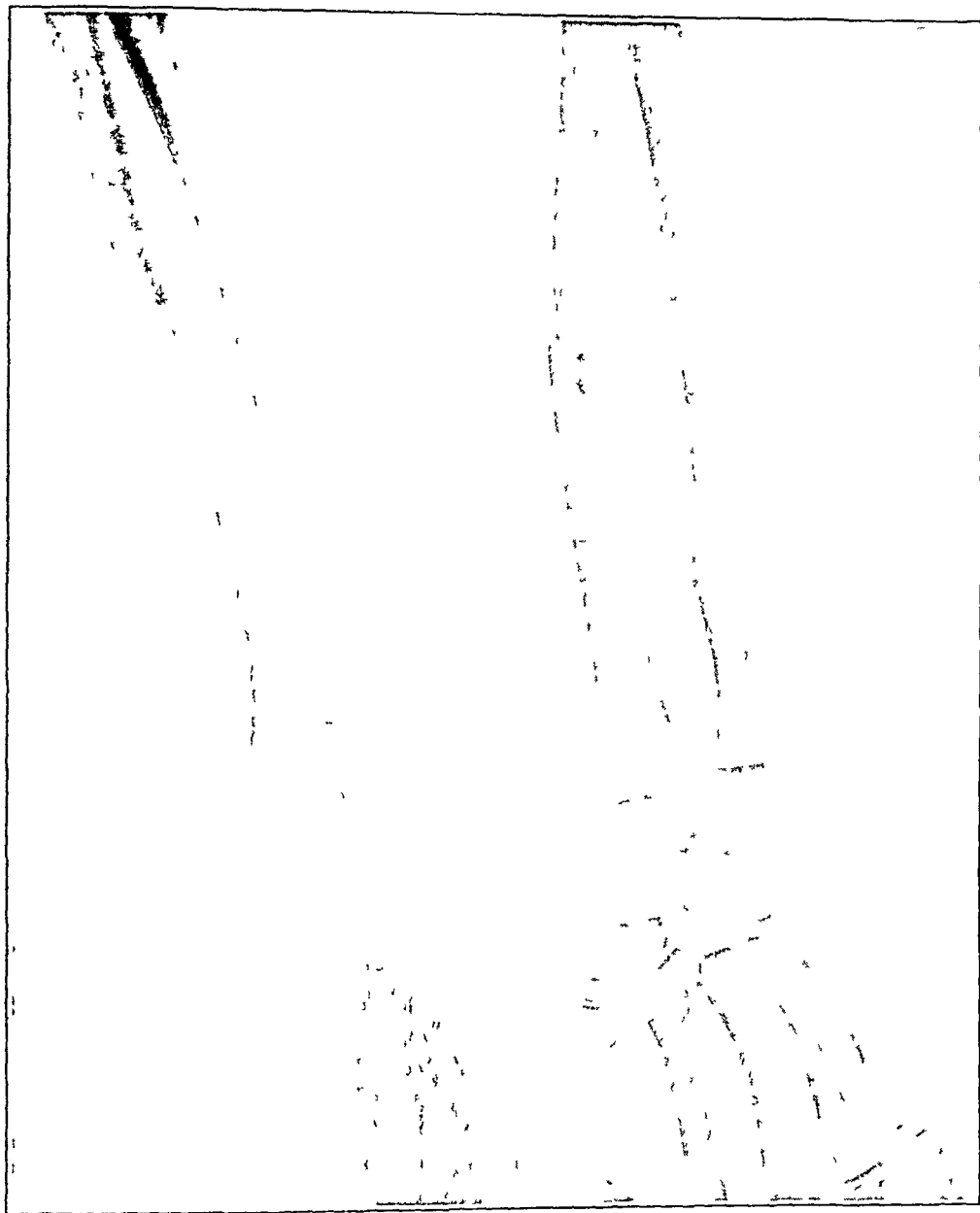


Fig 1—Roentgenograms of the left forearm immediately after the fracture was sustained The small bones, thin cortex and delicate structure are well shown The patient was 10 years old

Wassermann reaction of the blood was negative She was discharged from the hospital on August 20 In the dispensary viosterol was prescribed, and she was seen at intervals of several months

On Feb 3, 1932, she was brought again to the hospital, having sustained a compound fracture of the right forearm while roller skating Roentgen films

revealed a fracture of the lower end of the radius and a separation of the epiphysis of the ulna, fragments of both bones being displaced. With the patient under nitrous oxide anesthesia, the bones were satisfactorily reduced. The calcium content of the blood was 10.02 mg per hundred cubic centimeters, and the phosphorus content was 4.62 mg, both at the upper limits of normal. The child was discharged on February 8.

Scarcely had the splints been removed when the child fell, on April 15, and again sustained a compound fracture of the right forearm. Reduction was satis-

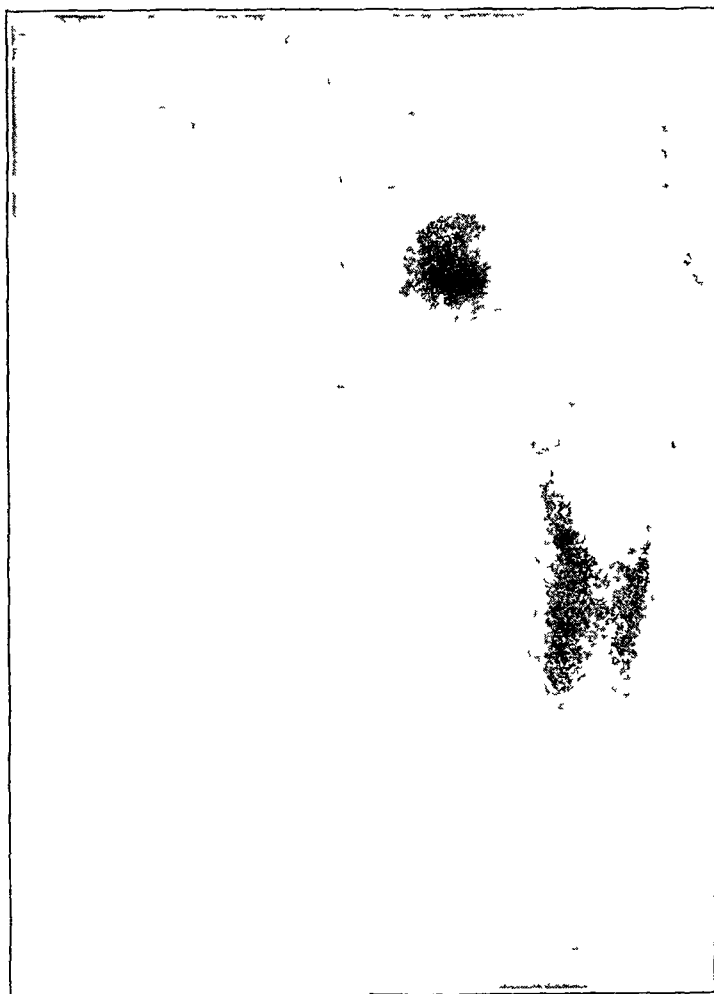


Fig 2—Posterior dislocation of the left hip following a simple fall to the pavement

factory, and she was allowed to return home. This was the fourth time that she had had a fracture of the forearm.

On May 14, only a month later, while jumping rope she fell to the ground and was unable to rise. When seen at the hospital she exhibited the characteristic signs of posterior dislocation of the left hip. A roentgenogram confirmed the diagnosis (fig 2). With the patient under nitrous oxide and ether anesthesia the dislocation was readily reduced, and a plaster spica was applied. The child was permitted to go home in three days, and the cast was removed in three weeks. She was allowed up on crutches and subsequently walked quite comfortably. On

August 8 she was seen again because of difficulty in walking. Examination revealed increasing relaxation of all the joints. The affected hip was still in proper position, but extended motion was painful. Roentgenograms revealed no abnormality except for some scoliosis and a consequent tilt of the pelvis.

The pain in the hip became worse, and on Feb 12, 1933, she was admitted to the Mercy Hospital. A diagnosis of arthritis of the hip was made. Manipulation of the joint was carried out, and she was placed in a spica cast, remaining in the hospital until October 27.

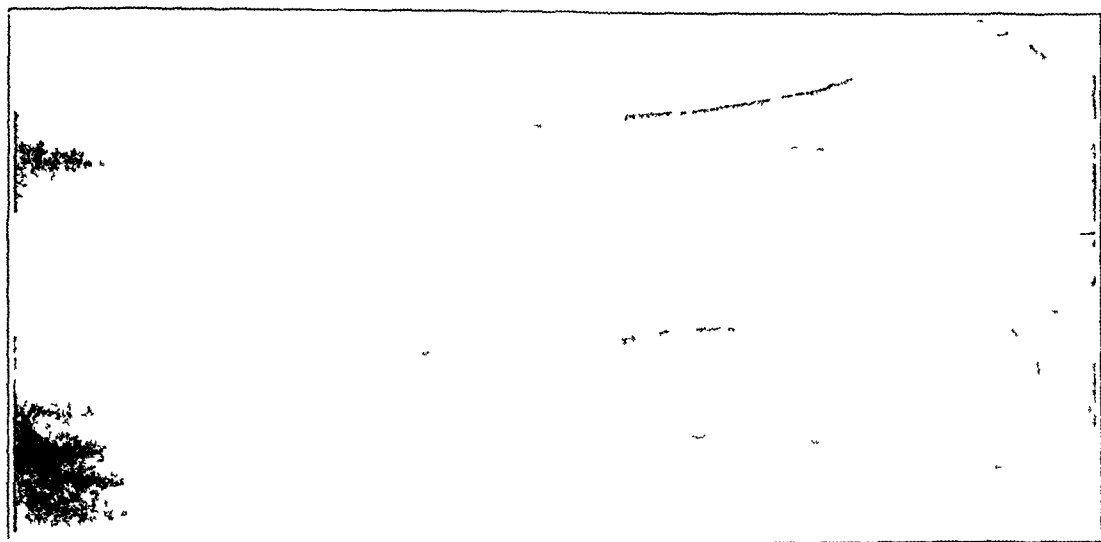


Fig 3—Roentgenograms of the right forearm which had been fractured on three different occasions. Union was prompt and solid in each instance. The osseous structure more nearly approached normal as puberty was reached. The patient was 15 years old.

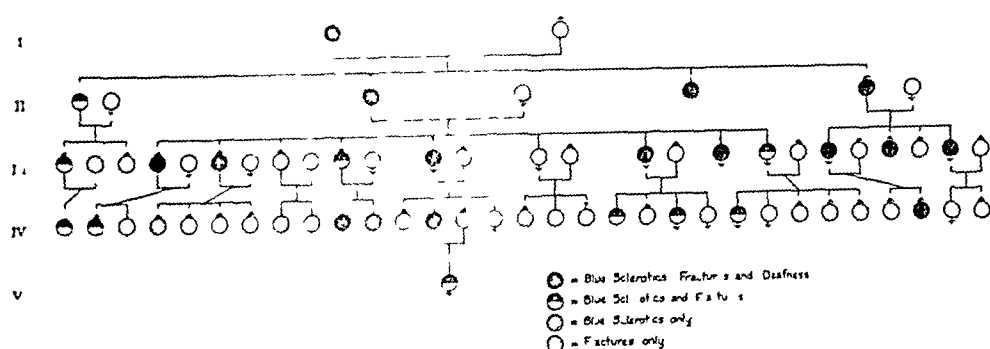


Fig 4—The family tree showing the appearance of characteristic signs in twenty-seven of the fifty-one members.

The hip continued to be painful, however, and walking was awkward, owing to a certain amount of ankylosis. On July 10, 1934, the patient was admitted to the Kernan Hospital for Crippled Children, where subtrochanteric osteotomy was performed by Dr. Albertus Cotton. She left the hospital on September 2. After convalescing from this procedure, the girl has walked without pain and has been quite comfortable, despite the fact that she has complete ankylosis of the left hip. There have been no more injuries. When examined by us in January 1936 she had grown and, though still slight of stature, looked well. The left hip was

ankylosed but gave comparatively little inconvenience, as she appeared to compensate well with the pelvis. We hope that puberty has brought freedom from fractures. Her mother is sensible, however, in refusing the girl's insistent requests for permission to play basketball and to own and use ice skates.

COMMENT

We were fortunate in being able to gain an accurate account of the family, and data were available concerning fifty-one members, including five generations with collaterals. All were traced back to a common ancestor, a woman. Twenty-seven members, approximately half, were affected. Striking is the fact that only one member of the group, a 3 year old child, had blue scleras but had broken no bones. This child is included in the accompanying chart. Sixty per cent of those affected were females. Deafness was manifest in 57 per cent, being more marked in the earlier generations. The incidence of deafness in the last two generations was only 25 per cent, illustrating its occurrence later in life. In no instance did an unaffected member give rise to an affected one. Successive generations revealed lower percentages of affected members. In studying the five persons in direct line, we noticed that all of them had demonstrated the three factors of the disease, with the exception of the 15 year old girl, the patient whose case has been detailed, who was not deaf. It can be predicted with almost certainty that otosclerosis will overtake her in the third or fourth decade of life. The findings in this family are in close agreement with the comprehensive statistics published by Bell.

It has interested us especially that we have been able to follow this child into adolescence and that there has been an apparent cessation of the fracture process, along with an improvement in physique. This observation, made many times before, might well give a lead as to the best therapy.

We believe that it is important that an affected person should be sensibly informed as to the facts of heredity in this disease, so that he may better face the difficult problems of marriage and having offspring.

CONCLUSIONS

This hereditary clinical entity is characterized by four distinct features: blue scleras, fragile bones, a tendency to deafness and marked relaxation of the ligaments.

It is to be distinguished from a large group of nonhereditary conditions associated with soft or brittle bones occurring at all ages and exhibiting many different etiologic factors.

This syndrome is best described as a hereditary hypoplasia of the mesenchyme and follows the mendelian law of inheritance, appearing as a dominant character.

Affected subjects are small. The blue sclerotics are generally attributed to thinness of the sclerotic coat, through which the choroid shines. The deafness is of an otosclerotic type.

The fractures are not likely to be present at birth but occur throughout childhood until puberty is reached. Union is as a rule prompt and complete.

The exact etiology is unknown. The pathologic changes have been carefully studied.

No method of treatment has been shown conclusively to be curative. New approaches along endocrine lines give the greatest promise of being helpful.

One case has been reported in detail. In addition, data have been presented on fifty other members of the same family, showing graphically the occurrence of the primary features of the disease in twenty-six of these.

Dr Sarah Peyton and Dr R. R. Norris, of Crisfield, Md., aided materially in obtaining data on the family history, and Dr Stacy R. Guild, of the Otolaryngological Department of the Johns Hopkins Medical School, cooperated in preparing the section on deafness.

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DIVERTICULUM OF THE PERICARDIUM

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Effusion into the pericardial cavity and inflammation of the pericardium are of frequent occurrence, and the diagnosis is usually made by clinical methods. Congenital absence of the pericardium and cyst of the pericardium have been noted at postmortem examination. A diverticulum of the pericardium, however, is unusual, and a clinical diagnosis has seldom been made. In some cases the diverticulum is probably of congenital origin. Bristowe, Atayas-Maraty, Seidler, Schirmer and Neprjachin have reported cases in which there was a large opening into the sac, with no evidence of a pathologic condition of the pericardium. There is no embryologic or anatomic explanation for the presence of an area of weakness in the pericardium. A traction diverticulum may occur (Luschka), with concomitant cardiac or pericardial disease. In cases of the latter type one may imagine that the pericardium had unusually thin fibers in one area or was weakened by disease and that increased intrapericardial pressure forced an out-pocketing through the fibrous layer. In one case the small opening connecting the diverticulum to the pericardium had been closed, possibly by further scarring of the pericardium (Atayas-Maraty). Pericardial diverticula have been described ranging from the size of a pea to that of a pear 12 cm long. It is interesting that in 52.5 per cent of the cases the diverticulum presented to the right. There is no pathologic explanation for this apparent area of weakness in the pericardium. Histologic examination of the wall of the diverticulum has shown it to be indistinguishable from the pericardium.

The clinical examination may lead one to suspect the presence of an enlarged heart or of a mediastinal tumor. The roentgenologic findings have been carefully studied by Kienbock and Weiss, who have described five cases. In one case the diverticulum was noted at postmortem examination, and that enabled the authors to make a diagnosis in the other four cases roentgenologically. They stated that an abnormal mass, rounded but with somewhat sharp sides, rests against the heart and pulsates. The roentgenographic picture can be confused with that of an aortic aneurysm or a dermoid cyst of the mediastinum. Jansson

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TABLE 1—*Data on the Location of Diverticulum of the Pericardium*

Position of Diverticulum	Number of Cases	Percentage of Cases
Right side of cardiac shadow	21	52.5
Left side of cardiac shadow	5	12.5
Anterior	5	12.5
Posterior	1	2.5
Lateral	2	5.0
No description	6	15.0

TABLE 2—*Data for Cases of Diverticulum of the Pericardium*

Author	Date	No of Cases	Clinical and Pathologic Findings	Cardiac or Pericardial Pathology	Description of Diverticulum
Hart, T	1837		Woman had anasarca, old adhesions in pleural cavity		Diverticulum in anterior portion of mediastinum, opening at point of reflection on aorta, sac contained 3 or 4 oz of fluid, opening admitted 1 finger
Hird	1848		65 year old patient	Vegetation of the mitral valves, surface of heart rough from old effusion of lymph	Pendent cyst connected to right side of pericardium with slitlike opening
Cruveilhier, J	1849		Aged woman, died of rupture of heart into pericardium		Hemispheric pocket in anterior, superior portion of pericardium
Rokitansky, K	1852	2	No information		Both on lateral part of pericardium
Luschka	1859	3	No information		Largest, size of walnut
Spir, S I	1865		Woman with palpitation	Palpitation	To left of pleural cavity, large diverticulum, "pericardium absent with arrested development"
Peacock, T B	1866		No information		Diverticulum 1 inch in diameter with tubular passage 1 inch long, small aperture to pericardial cavity, coats thin and transparent
Bristowe, J S	1867		Man, aged 47	Aortic and mitral disease confirmed at autopsy	Diverticulum in anterior portion of mediastinum, 1½ inches long, orifice oval, ⅓ inch long crescentic folds in diverticulum, congenital origin?
Cuffer	1875		Diabetic man		Diverticulum over inferior and posterior aspect of pericardium, protruding into mediastinum and connected with pericardial cavity
Baudy	1879		Postmortem examination sclerosis of aortic valves	Aortic sclerosis, heart enlarged, fibrous bands on outer surface	Diverticulum at right inferior surface of pericardium, sac contained 2 oz of fluid
Cocn, E	1885		Man aged 40, died of nephritis and uremia	Mitral stenosis and insufficiency, aortic insufficiency	Diverticulum, size of hen's egg, at right side of pericardium, circular opening, size of head of pin
Corsini	1890		Woman aged 20, died of typhoid and pulmonary complications		Cyst between anterior pulmonary artery and vein, started with tube 3 mm in diameter two appendages, 4.5 and 6 cm long, covered entire wall of heart, wall thin, microscopically wall was like pericardium

TABLE 2—Data for Cases of Diverticulum of the Pericardium—Continued

Author	Date	No of Cases	Clinical and Pathologic Findings	Cardiac or Pericardial Pathology	Description of Diverticulum
Atayas Maraty	1895		Postmortem examination diverticulum of congenital origin?		Diverticulum in anterior portion of mediastinum, 11 cm long, pear shaped, connected to pericardium by canal 2 cm by 8 mm, did not open into pericardial cavity, contained 80 cc clear lemon yellow fluid, histologic examination structure comparable to that of pericardium
Piazza Martini	1895		Man aged 23 died of cardiac failure	Heart bilaterally enlarged	"Cyst" in upper anterior part of pericardium, connected with pericardium, containing same clear fluid
Schrotter, L	1901		Pericarditis following Bright's disease		Diverticulum, size of hen's egg, protruded into right lung, filled with serous fluid
Rohn, A	1903	4	(a) Woman aged 40	(a) Mitral stenosis and insufficiency, pericardial effusion	(a) Diverticulum 7 cm long with 9 mm circular opening (b) Diverticulum to right, 4.5 by 4 cm, circular opening (c) Diverticulum opening to left 4.5 by 2 cm (d) Diverticulum opening to left 1 by 2 cm, with 4 mm opening posterior
Sehgenti, W	1921		Pericarditis		Diverticulum, 8.5 by 5.5 by 3.5 cm, wall resembled thin pericardium
Seidler, E	1921		Woman aged 63, blood pressure 250/170, died of apoplexy	X ray plate showed mass to right of heart, aneurysm or dilated aorta? probably congenital	Diverticulum size of hen's egg to right
Schirmer, O	1923		Woman aged 40 generalized tuberculosis and Pott's disease		Two diverticula to right (1) 2.5 by 2 by 1 cm with 7 mm opening, (2) 8 by 9 by 4 mm, probably congenital in origin
Lauer, W	1925		Man aged 30 insane, pulmonary tuberculosis		Diverticulum near right auricle, 8 by 6 by 4 cm, containing 5 cc clear fluid, wall like pericardium but thinner resembled Meckel's diverticulum
Grabowski, W	1926		Woman aged 50	Syphilitic aortitis and aortic dilatation with resulting aortic insufficiency	Diverticulum at anterior aspect and more to right 3.8 by 2.2 by 2 cm with probe sized opening into pericardium
Neprijachin, G	1927		Man aged 32 pulmonary tuberculosis	Fibrous endocarditis	Diverticulum 1.8 by 1.5 by 6 cm with pencil sized opening into pericardium extended to right, by right auricle, congenital origin?
Kedrovsky, V V	1929		Woman aged 47 with mitral stenosis	X ray plate showed heart enlarged to right, with diverticulum seen as triangular shadow	Diverticulum to right 5.5 by 2 cm with oval opening 3.5 cm in diameter

TABLE 2—Data for Cases of Diverticulum of the Pericardium—Continued

Author	Date	No of Cases	Clinical and Pathologic Findings	Cardiac or Pericardial Pathology	Description of Diverticulum
Kienbock, R, and Weiss, K	1929	3	(a) Woman aged 39, followed for 21 years, at 58 years, pulsating tumor to right of pericardium, 13 years after diagnosis of aneurysm (b) Man aged 33 (c) Woman aged 37, followed for 3 years, clinical question of tumor or aneurysm, diverticulum present post mortem, diagnosis in previous two cases then made		Diverticulum to right, \ ray diagnosis Diverticulum to right, \ ray diagnosis
Jansson, G	1931		Patient followed for 2 years, no change		Diverticulum to right, \ ray diagnosis, rounded shadow to right of pericardium
Wiese, O	1931		Man aged 20		X ray diagnosis by Kienbock, diverticulum extended to right
Ypsilanti, H	1931		Man aged 34 with pulmonary tuberculosis, dementia praecox		Diverticulum 9 by 3 by 4 cm at right lower end of pericardium, indistinguishable from pericardium
Juderholm, K G	1932	2	(a) A 54 year old patient (b) Woman aged 52 with mitral stenosis, question of interlobar pleurisy, died of cardiac decompensation proved diverticulum at necropsy		Diverticulum to right, extending into lung field Diverticulum to right, with opening the size of pencil into pericardial cavity near base of right lung close to mediastinum
Kienbock, R, and Weiss, K	1932				Reports cases a, b and c, as in 1929 to right and new case, d, with diverticulum to left, \ ray diagnosis
Kienbock, R, and Weiss, K	1934		(a) Further report on first patient, now 66 years of age, diverticulum showed calcification (c) Man aged 42 with calcified diverticulum		Diverticulum to right, \ ray diagnosis

added another helpful observation by stating that on deep inspiration the shadow becomes long and narrow and with expiration, rounder, shorter and broader

Beck and Cushing reported nine cases in which there was evidence of increased intrapericardial pressure. The fourth patient in that series was studied in 1931, and roentgenographic examination showed a mass suggestive of an encapsulated pericardial effusion or an aneurysm and definite deposits of calcium in the pericardium. This patient could not be followed and was not seen until July 1935, when he appeared in the dispensary and stated that a nontender mass had appeared on the left side of the chest, close to the "breast bone"

REPORT OF A CASE

A 43 year old Negro laborer had been treated in 1925 for a gumma of the leg. Six years later he reappeared in the outpatient department with the complaint of an aching pain in the right side of the chest which was accentuated by activity and by lying on that side. There were marked distention of the veins of the neck, enlargement of the heart, especially to the right of the sternum, and occasionally extrasystoles. There was no Broadbent sign or pulsus paradoxus. There was no ascites, and the liver was not palpable. The arterial pressure was 136 mm of mercury systolic and 80 mm of mercury diastolic. The venous pressure was 22 cm of physiologic solution of sodium chloride. Roentgenograms showed enlargement of the heart, with indefinite pulsation. A mass (fig 1) suggestive of an encapsulated pericardial effusion or an aneurysm was present which displaced the heart



Fig 1—A roentgenogram showing widening of the right cardiac outline and calcification in this area

backward and to the left. The pericardium showed definite deposits of calcium. A dextrocardiogram was slightly irregular, with occasional ventricular premature beats. The voltage was normal.

The patient was next seen in the dispensary in July 1935. He stated that about eighteen months previously he had noted a nontender swelling to the right of the sternum (fig 2), which had steadily increased in size in spite of repeated aspiration of clear yellow fluid by his physician. There had been increased dyspnea on exertion during the past year. Physical examination revealed a soft, fluctuant, nontender mass, 8 cm in diameter and 4 cm in height, between the third and the fifth rib to the right of the sternum. The swelling pulsated with cardiac systole, but there was no thrill. The heart sounds could be well heard over this area. The heart was enlarged to the left, and a systolic murmur was heard at the apex.

The blood pressure was 126 systolic and 100 diastolic in both arms. The remainder of the examination revealed no abnormality. Roentgenographic and fluoroscopic examination showed little change from the plates made four years previously. There was possibly a trifle more calcification in the pericardium. The venous pressure was 400 mm of water. The 180 cc of yellowish fluid which was withdrawn showed some involuted acid-fast forms, and inoculation of this fluid into guinea-pigs produced typical acid-fast lesions, causing their death. Inspiration and expiration caused changes in pressure on the manometer which was attached to the tumor, and cardiac systoles also were recorded on the manometer. Fifty cubic centimeters of air was injected into the tumor, and a roentgenogram showed part of the air to be in the pericardial cavity and part beneath the skin (fig 3). An unsuccessful attempt was made to inject more air in order to outline the pericardium properly.

While the patient was in the hospital auricular flutter developed, but digitalis produced a normal rhythm. The patient felt much better after aspiration of fluid and was discharged, to be followed in the dispensary.

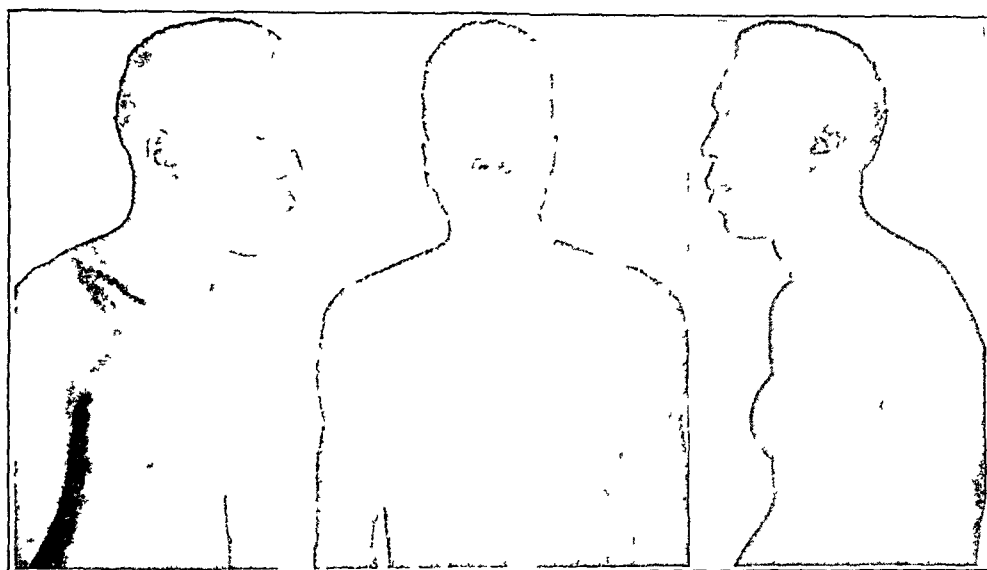


Fig 2—Photographs showing the mass to the right of the sternum

The patient was readmitted to the hospital on Dec 3, 1935. He stated that he had been well and had had no swelling of the chest or shortness of breath. A week before his readmission to the hospital he had a cold, and the swelling reappeared on the chest. He complained of weakness, nausea and vomiting. There was evidence of retention of food eaten at least six hours previously. Physical examination showed no change in the past six months. Fluoroscopic examination of the stomach showed evidence of an ulcer niche about 1.4 cm in width and 0.08 cm deep. The patient was placed on a Sippy diet and atropine, which controlled the gastro-intestinal symptoms. A second fluoroscopic examination made four weeks later showed that the ulcer had disappeared.

The pericardial diverticulum was aspirated twice, and 50 and 45 cc, respectively, of thin, brownish fluid was removed. Smears showed no tubercle bacilli. The intrapericardial pressure fell from 12 cm of water to 0 at the end of the tap, and the venous pressure dropped from 15 cm of a 0.25 per cent solution of sodium citrate to 13 cm. There was no change in the blood pressure or in the patient's condition at the end of the procedure.

Air was again injected into the diverticulum and again could be seen in the pericardial cavity. Thickening of the pericardium could be seen over the base of the heart.

Electrocardiograms showed an elevated T wave in the fourth lead. Otherwise there was no abnormality. Removal of fluid from the pericardial diverticulum did not alter the electrocardiographic picture, and the electrical axis did not change.

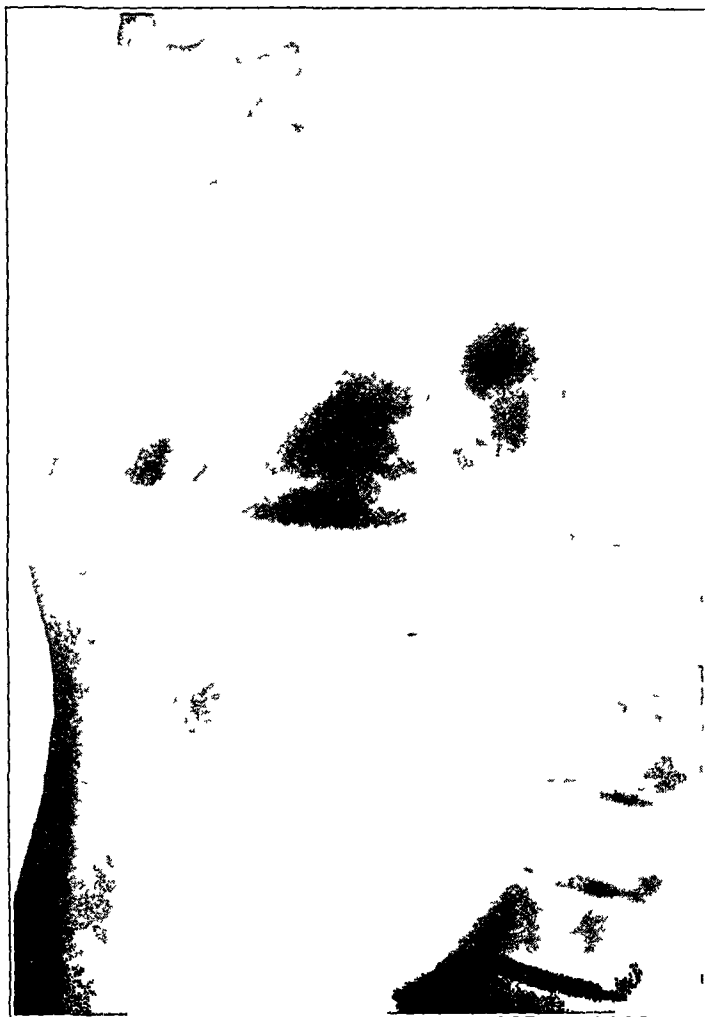


Fig 3—Air is present in the subcutaneous mass and in the pericardial cavity. Note the thickness of the pericardium and the calcification.

COMMENT

This case is the first described in which a pericardial diverticulum has presented on the anterior wall of the chest. The diagnosis was confirmed by injecting air into the subcutaneous mass and finding air within the pericardial cavity. The roentgenographic findings were typical of those in the cases described by Kienbock and Weiss and by Jansson. The diagnosis of calcified tuberculous pericarditis was con-

firmed by the demonstration of tubercle bacilli in the pericardial fluid obtained by aspirating the diverticulum and by the death from tuberculosis of guinea-pigs inoculated with the fluid

SUMMARY

Thirty-nine cases of diverticulum of the pericardium have been described in the literature, and one additional case is reported here

NOTE —An additional case of pericardial diverticulum on the right side was described by Einst, with the typical shadow shown to the right side of the heart in the roentgenogram

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PATHOGENESIS OF ERYTHEMA NODOSUM

WITH SPECIAL REFERENCE TO TUBERCULOSIS, STREPTOCOCCIC
INFECTION AND RHEUMATIC FEVER

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Considerable attention has been directed in recent years to the etiology of erythema nodosum. Various explanations for this cutaneous eruption have been given and include the following: (1) It is a manifestation of tuberculosis, (2) it occurs as part of the symptom complex of rheumatic fever, (3) it has its origin in streptococcic infection, (4) it is a specific infectious disease the etiology of which is not known, and (5) it may occur during the course of various infections, and any one of a number of toxic and bacterial agents may be the cause, including the tubercle bacillus and the hemolytic streptococcus.

While most writers appear to accept the tuberculous concept of erythema nodosum, my colleagues and I have been impressed by the close association which the appearance of this eruption has with streptococcic infections. Because of the apparent confusion in the literature and our own previous observations, the following studies were carried out. My purpose here is to point out that erythema nodosum is a nonspecific inflammatory reaction of the skin due to a variety of agents, including the tubercle bacillus and the streptococcus.

METHODS

In addition to a review of the literature, two methods of approach were followed in this study. First, clinical and experimental studies were carried out on ten patients with erythema nodosum. These included nine females and one male. In an endeavor to elicit any precipitating factor in the patient's illness the following means were employed. A careful history was obtained in each case with particular reference to any recent infection or exposure to tuberculosis, repeated roentgenologic examinations of the lungs were made, and when sputum could be obtained examination was made for the tubercle bacillus, for patients in whom rheumatic fever was suspected, at least one electrocardiogram was taken, and repeated observations were made of the sedimentation rate of the erythrocytes, cultures of material from the nose and throat were studied by the pour plate method for hemolytic streptococci, aerobic cultures were made of venous blood also, teeth

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with clinical or roentgenologic evidence of infection were extracted, and cultures were made of material from the roots and the cavities immediately after extraction. In addition, intradermal tests were performed for each patient with the scarlatinal streptococcus exotoxin, a scarlatinal streptococcus endotoxin (nucleoprotein fraction) and tuberculin in varying amounts. When a hemolytic streptococcus was isolated from either the nose or the throat, a broth filtrate of the organism was prepared and injected intradermally into the patient. Histologic examinations were made of biopsy specimens of spontaneous nodes and of nodes due to the injection of tuberculin and streptococcus nucleoprotein.

The second method of approach was by means of an analysis of the records of one hundred and thirty-three patients treated for erythema nodosum at the Boston City Hospital from 1924 to 1934.

RESULTS OF CLINICAL OBSERVATIONS

Evidence for Tuberculosis—As far as could be determined, in none of the cases was there a causal relationship between exposure to tuberculosis and the development of erythema nodosum. Repeated roentgenologic examinations of the lungs showed no tuberculous involvement of either the parenchyma or the hilar glands. Mantoux tuberculin tests gave the following results: one positive reaction with 0.001 mg., one with 0.005 mg., three with 0.01 mg. and one with 0.1 mg. In no instance did the injection of tuberculin result in a systemic reaction or the appearance of more nodes. In two cases the tuberculin nodules were slightly tender but pinkish rather than red like the lesions of erythema nodosum. Although the period of observation was less than a year for most of the patients, none showed evidence of tuberculosis.

The following case history illustrates the difficulty encountered in distinguishing between tuberculosis and acute rheumatic fever in a person with erythema nodosum.

R. N., a 16 year old girl, first entered the hospital in June 1934. She had been treated for several years for bronchial asthma. One week before entry she complained of headache and general malaise. Five days later a painful eruption appeared on the anterior surface of the lower part of the legs which was typical of erythema nodosum. Twenty-four hours before entry she had four severe nose-bleeds. The cutaneous lesions on the legs gradually disappeared. Soon after she entered the hospital phlyctenular conjunctivitis developed and subsided with local treatment. Because erythema nodosum and phlyctenular conjunctivitis may be associated with tuberculosis, several roentgenograms of the chest were taken, but no lesions were observed. The sedimentation rate was normal three weeks after her entry into the hospital, and she was discharged one week later. She complained of twinges of pain in the joints on walking. She was advised to limit her activities and did so.

Six months after her discharge she reentered the hospital because of chills, fever and migrating polyarthritides. Two weeks later there were signs of fluid at the base of the left lung, and 8 cc. of cloudy, pink fluid, having the characteristics of a transudate, was removed. Guinea-pig inoculation with the fluid showed no evidence of tuberculosis six weeks later. The articular pain and fever subsided.

while salicylates were given, and when the latter were omitted because of toxic symptoms, there was an exacerbation of the pain. After the removal of fluid from the left pleural cavity, repeated roentgenologic examinations of the pulmonary fields revealed no abnormality except slight deformity of the heart. Electrocardiograms also were within normal limits. The Mantoux tuberculin and streptococcus nucleoprotein cutaneous tests showed positive results. While the patient was under observation, the character of the heart sounds changed and was thought to be consistent with an early stage of endocarditis. The pulse rate continued to be elevated. The patient was discharged eleven weeks after entry, with the diagnosis of an early stage of rheumatic endocarditis.

The patient immediately entered a sanatorium for patients convalescing from rheumatic fever, where she remained for five and a half months. The sedimentation rate of the erythrocytes was persistently elevated. The patient had intermittent mild attacks of arthritis. There was no essential change in the cardiac signs. She was discharged with the diagnosis of rheumatic fever (?) and potential rheumatic heart disease.

The patient was free from symptoms at home for one month and then complained of pain in the left axillary region. Examination of the chest showed signs consistent with fluid in the left pleural cavity. It had the characteristics of a transudate. Inoculation of guinea-pigs with the fluid has not given evidence of tuberculosis up to the present time. The patient has presented no further evidence of rheumatic heart disease, and the effusion is considered as due to a tuberculous infection until proved otherwise. Subsequently, in guinea-pigs inoculated with the pleural fluid tuberculosis developed. Roentgenograms of the patient's pulmonary fields showed no parenchymatous lesions. Since she had pleurisy with effusion on a tuberculous basis, she was sent to a sanatorium for tuberculous patients.

Evidence for Streptococcus Haemolyticus—Erythema nodosum was preceded shortly by sore throat in five of the ten patients. One patient had had erythema nodosum three years previously after a severe sore throat. Two patients had sore throats and painful joints. Culture of material from the throat in four cases revealed *Str. haemolyticus* of the beta type. One-hundredth milligram of the streptococcus nucleoprotein fraction injected intradermally gave marked reactions in eight of the ten patients. The resulting lesions varied in size from 2 to 5 cm, were red and tender and could not be distinguished from the early lesions of erythema nodosum. They appeared from twelve to twenty-four hours after the injection. In two patients a systemic reaction followed the injection, with fever and the appearance of several new lesions on the extremities.

In order to ascertain whether any local immunity to the endotoxin of the streptococcus had developed at the site of the lesion of erythema nodosum, 0.01 mg. of streptococcus nucleoprotein was injected into a node three or four days old. A similar amount was injected into an area of normal skin. The reaction in the node was much less than that in the skin. The same procedure was carried out by injecting

the same amount of nucleoprotein into the lesion produced by a previous injection of nucleoprotein. Again the reaction was much less than that of normal skin.

A filtrate of *Str. haemolyticus* of the beta type from two patients was prepared by growing the organism isolated from the throat in ordinary broth for twenty-four hours. It was then put through a Berkefeld filter, and saline dilutions were made of the filtrate. One-tenth cubic centimeter of 1:100 and 1:10 dilutions and 0.1 cc of the undiluted filtrate were injected intradermally into each of the patients. In one case there was no reaction with the diluted filtrates, but there was a slight reaction twenty-four hours later with the undiluted filtrate. The second patient showed an elevated erythematous reaction 2 cm in diameter with the 1:100 dilution and a reaction 4 or 5 cm in diameter with the 1:10 dilution and the undiluted filtrate. These lesions were very painful and were similar to the lesions of erythema nodosum on this patient's extremities. This patient was highly sensitive to both the exotoxin and the endotoxin of the streptococcus, and the attack of erythema nodosum was the second one she had had in three years, each one having followed a severe sore throat. Unfortunately, a Dick test was not performed. The remainder of the patients all showed a negative reaction to the Dick test.

It is of interest that the morbidity rate for tuberculous and streptococcal infections is relatively high among the student nurses of the Boston City Hospital. During the past two years there have been only two cases of erythema nodosum among six hundred nurses; these occurred in young women who had severe streptococcal infection of the throat. The following case history is that of one of these nurses.

E. V., a 21 year old student nurse, was first seen in December 1933, when she had a typical attack of tonsillitis. Six months later she entered the hospital because of a herpetic lesion at the site of the exit of the right infra-orbital nerve. Four weeks later she entered the hospital for the third time, because of acute follicular tonsillitis. She complained of pain along the right costal margin. However, repeated roentgenologic studies of the lungs revealed no abnormality. Cultures of material from the throat revealed *Str. haemolyticus* of the beta type. Although she was asymptomatic in a week, her throat continued to show streptococci for a month. She was treated as a carrier and sent home. One month after her discharge, cultures of material from the throat showed no streptococci with beta hemolysis. She entered the hospital for the fourth time six months later. She had had a sore throat two weeks before. Four days before entry she had acute polyarthritis, and the following day the typical lesions of erythema nodosum appeared on the lower portion of the legs. The patient responded well to salicylates. The sedimentation rate was normal throughout the course of the illness. Electrocardiograms were normal, and roentgenograms of the chest were within normal limits. Culture of material from the throat showed *Str. haemolyticus* of the beta type. A Dick test showed a negative reaction. Injection of 0.01 mg of

nucleoprotein intradermally resulted in a typical painful erythematous node at the site of the injection on the forearm, which could not be distinguished from the lesions on the leg. An intradermal injection of 0.05 mg of tuberculin gave a positive reaction, but this was less severe and painful and pale pink.

The patient made an uneventful recovery, but tonsillectomy was performed six months before this article was written because of repeated attacks of tonsillitis. She has been in good health since then.

Other Etiologic Factors—There were three females with erythema nodosum who showed no evidence of preceding infection of the upper respiratory tract or of tuberculosis. However, each patient stated that she had an "abscessed tooth" shortly before the eruption developed.

In one case painful nodules appeared shortly after the extraction of a tooth which showed evidence of infection about its roots. In a second patient there was swelling of the left side of the face, due to an infection about a molar tooth, five days before the appearance of erythema nodosum. Cutaneous tests with the streptococcus nucleoprotein and tuberculin showed a marked reaction to the former and a negative reaction to the latter. Roentgenograms of the teeth revealed periapical infection of the right second bicuspid and lower left first molar teeth. These were extracted, and cultures were made of material from the cavities and from the roots of the cystic teeth. The only organism recovered was *Staphylococcus albus*. In the third patient erythema nodosum developed after the patient had been in the hospital for three and a half weeks. She had entered because of a fractured leg. There were no other patients with erythema nodosum in the hospital at the time. The patient was not placed in isolation, and in no one attending her and in no other patient did erythema nodosum develop. The patient showed marked local and systemic reactions to the intradermal injection of streptococcus nucleoprotein. The tuberculin test gave a negative result.

HISTOLOGIC EXAMINATION OF THE NODULES

A nodule was excised from the lower portion of the leg of each of two patients with erythema nodosum, one having a streptococcal infection of the throat and the other an infection about the root of a tooth. The lesions were four or five days old. The tissues were fixed in Zenker's solution and stained with eosin and methylene blue. At the same time biopsy specimens from lesions in the same patients resulting from the intradermal injection of streptococcus nucleoprotein were fixed and stained in the same manner. These lesions were twenty-four hours old. Microscopic examination of the two types of lesions showed them to be similar histologically. The only distinguishing feature between the two was that the twenty-four hour old artificial node showed evidence of an acute reaction, whereas the reaction of the four day old lesion of erythema nodosum was beginning to subside. Figures 1 and 2 are low power photomicrographs of the twenty-four hour and four day lesions, respectively.

Microscopic examination of the four day lesion of erythema nodosum showed that the epidermis was intact. There was focal infiltration of cells in the reticulum

of the derma which extended into the hypodermis. There was edema of the collagen bundles in the derma. The cellular infiltration in the hypodermis consisted mostly of lymphocytes, with a few polymorphonuclear leukocytes and rare eosinophils. The infiltration was perivascular, with the vessels dilated. The area illustrated in figure 1 was deep in the hypodermis, showing a destruction of collagenous and fibrous tissue, with polymorphonuclear leukocytes predominating. Many of the latter cells had pyknotic nuclei.

Examination of the twenty-four hour node due to the injection of nucleoprotein showed that the epidermis was intact. The focal cellular infiltration was more

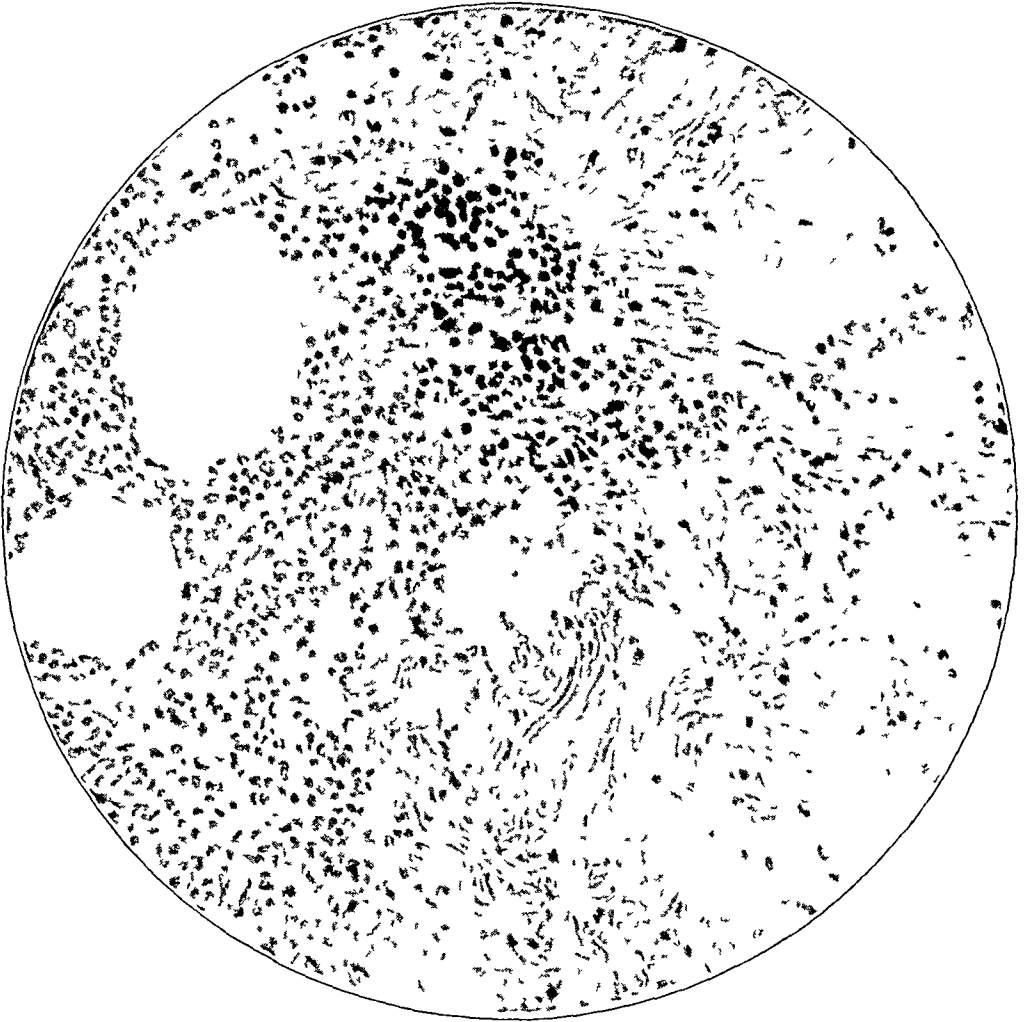


Fig 1—Section of a cutaneous lesion from a patient with erythema nodosum twenty-four hours after the intradermal injection of streptococcus nucleoprotein, showing edema of the tissue and round cell infiltration, $\times 215$

extensive. There was edema of the collagenous tissue. Just under the epidermis was a longitudinal area of cellular infiltration with dilated vessels and also infiltration with young fibroblasts. The cells were mostly lymphocytes, with some polymorphonuclear leukocytes. The areas of focal infiltration were perivascular, with some destruction of adjacent collagenous tissue. Extending down the strands of reticulum into the subcutaneous fat tissue was considerable cellular infiltration.

Figure 2 illustrates a section taken from within the derma, showing edema of collagenous tissue, dilated vessels and cellular infiltration, mostly of the lymphocytic series

A comparative histologic examination was made of excised lesions due to tuberculin injected intradermally and streptococcus nucleoprotein obtained from an arthritic patient without evidence of either tuberculosis

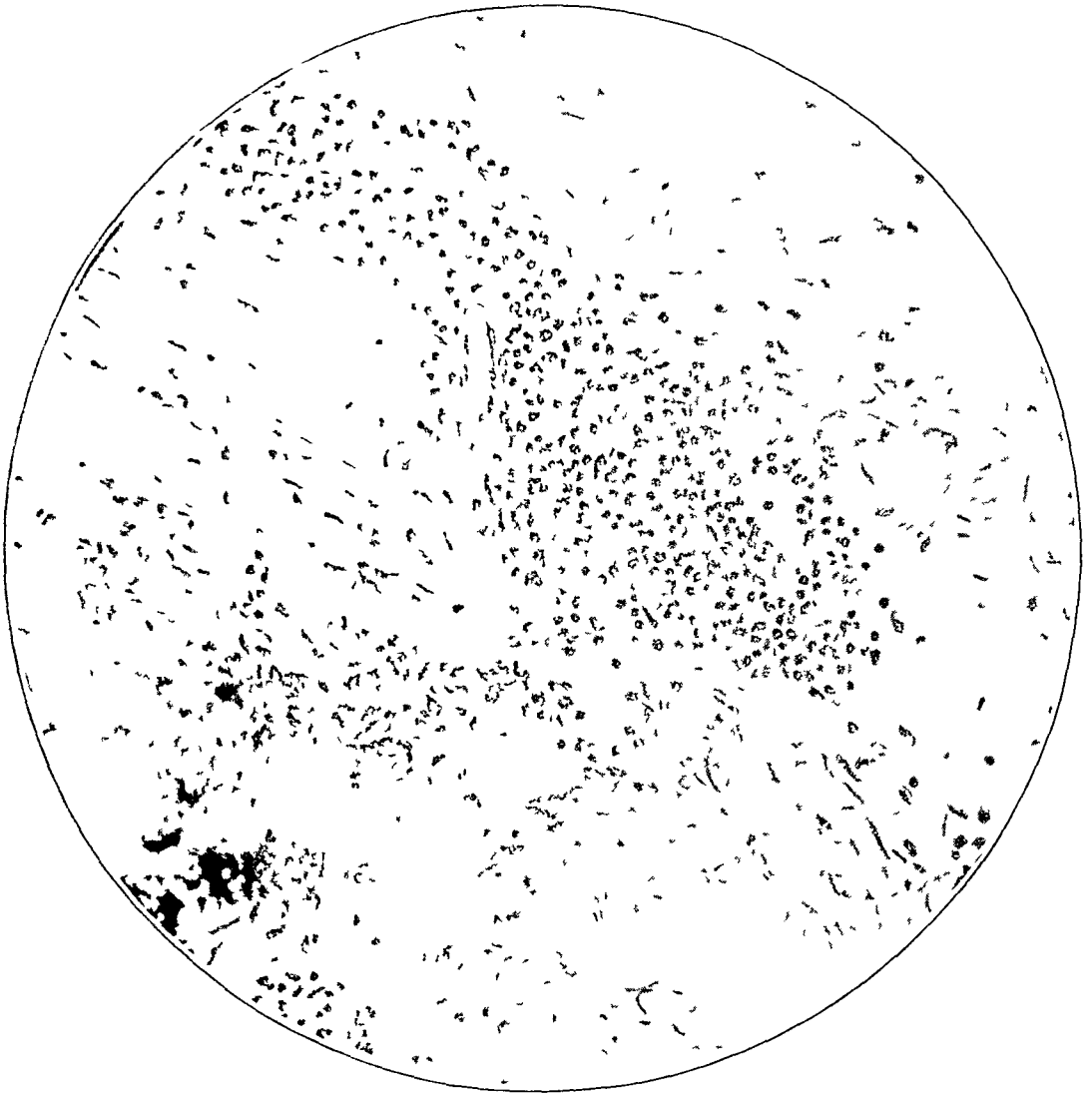


Fig 2—Section of a cutaneous lesion of erythema nodosum (four days old) showing edema of the tissue, round cell infiltration and slight necrosis of the tissue, $\times 215$

or erythema nodosum. The reaction in the tissues was essentially the same as that just described.

Briefly, then, the same type of cellular and tissue reactions was observed in the excised lesions of erythema nodosum as those resulting from the intradermal injections of tuberculin and streptococcus nucleoprotein.

ANALYSIS OF ONE HUNDRED AND THIRTY-THREE CASES OF
ERYTHEMA NODOSUM

Age Incidence—From 1924 to 1934, inclusive, one hundred and thirty-three patients were treated at the Boston City Hospital for erythema nodosum. There were one hundred and eleven females and twenty-two males. Figure 3 shows that the highest incidence of the disease was in females between the ages of 20 and 29 years. Before puberty the sex incidence was about evenly distributed, but after that there was a sharp increase in the number of females. This sex and age distribution is in agreement with reports in the literature.

Seasonal Incidence—Figure 4 illustrates the seasonal incidence of the cases. The greatest number of cases occurred in the early spring,

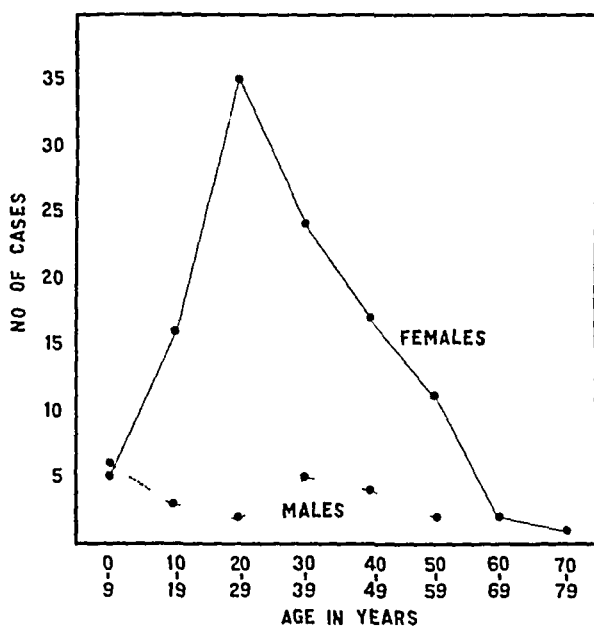


Fig 3—Graph showing the age and sex incidence in one hundred and thirty-three cases of erythema nodosum

the incidence reaching a low level in midsummer and gradually rising early in the fall. Figure 4 shows data for the seasonal incidence of a known streptococcic infection, acute follicular tonsillitis, of which there were ninety-five cases, with *Str. haemolyticus* of the beta type isolated from the throat in each case. It is seen that the curve of this streptococcic infection closely approximates that of erythema nodosum. Other streptococcic infections, such as scarlet fever and erysipelas, have the same seasonal incidence as tonsillitis. This relationship is not offered as definite proof that erythema nodosum is a manifestation of a streptococcic infection, but it must be considered along with other data presented in this study.

Relationship to Streptococcic Infections and Rheumatic Heart Disease—Erythema nodosum followed the exposure of several of the patients to streptococcic infection in other members of their respective families. There were forty-one patients (30·8 per cent) who had tonsillitis or acute pharyngitis either before or during the eruption. Fifty-five patients (41·3 per cent) complained of painful joints. Twenty patients (15 per cent) had both a sore throat and painful joints. Because of the latter symptoms and the high incidence of rheumatic fever in New England, that diagnosis was entertained in many of the cases. A series of electrocardiograms was obtained for thirty patients. Twenty-seven revealed no abnormality; there was a prolonged P-R interval in two, and one showed evidence of myocardial disease. Six of the patients with painful joints had definite clinical evidence of rheumatic valvular endocarditis.

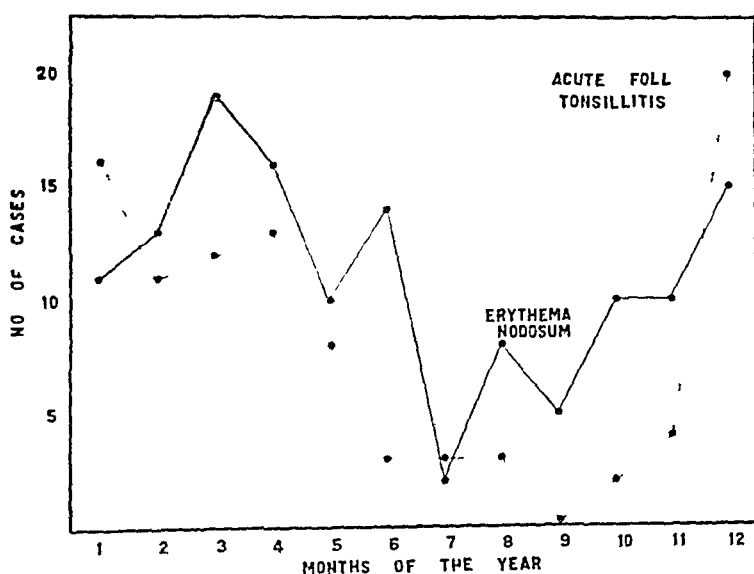


Fig. 4—Graph showing the seasonal incidence in one hundred and thirty-three cases of erythema nodosum and ninety-five cases of acute follicular tonsillitis.

Considering the state of the heart in more detail, one notes that fifteen patients (11·2 per cent) had rheumatic heart disease. There were five cases of mitral stenosis, nine of mitral stenosis and regurgitation and one of both mitral and aortic stenosis and regurgitation. There was one case each of congenital heart disease and hypertensive heart disease.

One patient entered the hospital with erythema nodosum, Sydenham's chorea and mitral valvulitis. Another patient had been sent to a sanatorium because tuberculosis was suspected. Two months later she entered the Boston City Hospital with erythema nodosum and early rheumatic mitral valvulitis. There was no evidence of tuberculosis.

Relationship to Tuberculosis—In only two instances was it recorded that erythema nodosum followed exposure to tuberculosis. One patient had been married for nine months to a man with advanced tuberculosis. She had an abortion three months after marriage. No clinical or laboratory evidence could be found for tuberculosis. A second woman had been exposed to a sister with tuberculosis. One examination of the sputum revealed tubercle bacilli, but eleven successive examinations, including a study of two concentrates, gave negative results. Roentgenologic examination showed patchy density at the base of the left lung.

Intradermal tuberculin tests were made in only eleven cases. In four there was a positive reaction and in seven a negative reaction.

Roentgenologic examination of the lungs was carried out in forty-eight cases, and the findings are summarized as follows:

	Cases
Lungs within normal limits	30
Cloudy patch at base of left lung	2
Bronchitic thickening	3
Congestive cardiac changes	3
Enlargement of hilar lymph nodes	3
Old calcified tuberculosis of lungs	2
Abscess in upper lobe of right lung	1
Bronchiectasis	1
Slight clouding of apex of left lung, "not enough for tuberculosis"	1
Fine infiltration in the left side of chest (bronchopneumonia)	1
Enlargement of thymus	1

Before drawing any final conclusions as to the relationship between tuberculosis and erythema nodosum in this series of cases, it is desirable to consider the follow-up study. This study was accomplished in part, as several of the patients had a recurrent attack and returned to the hospital for treatment. A check-up of the remainder of the patients was impossible for there were no available records of their present addresses.

Recurrent Attacks of Erythema Nodosum—There were eleven patients (83 per cent) who had had previous attacks of erythema nodosum from four weeks to fifteen years previously. Roentgenologic studies revealed that only one of these patients showed any changes in the lungs (mottling at the apex of the left lung but "not enough for tuberculosis"). The sputum showed no acid-fast bacilli at several examinations. Two of the patients had a double mitral lesion on a rheumatic basis, one having had erythema nodosum with articular pains seven years previously. At that time there was no evidence of endocarditis. Four of the patients had had preceding infection of the upper respiratory tract, and one had had otitis media which required drainage.

Other Etiologic Factors—In two cases erythema nodosum developed during convalescence from measles. In three other cases there were cutaneous lesions in association with dental abscesses which required extraction of teeth. Of considerable interest was a man who had gonococcic septicemia and erythema nodosum and who finally made a complete recovery.¹

It appears, then, from our observations that streptococcic infections play a more important rôle in the etiology of erythema nodosum than tuberculosis. Other workers have not found this same association, and they have emphasized repeatedly that erythema nodosum is a manifestation of tuberculosis. In order to correlate our findings with those of others, the literature on the subject has been reviewed.

Since the tuberculous origin of erythema nodosum is the theory having the most numerous adherents, it will be discussed first. Acceptance of this theory is based on the following observations:

1 The tubercle bacillus has been observed microscopically in the excised lesions of erythema nodosum, and injection of these nodules into animals has caused tuberculosis.² An acid-fast bacillus has been isolated from the venous blood of patients with erythema nodosum.³

2 Definite clinical evidence of tuberculosis has been demonstrated in patients with erythema nodosum. This has been observed especially in children by Einberg⁴ and Wallgren⁵ in Sweden and by Dickey⁶ and Hess and Berman⁷ in this country. In Copenhagen erythema nodosum was found to occur almost as frequently as pleurisy in persons

1 This case was reported in detail by Drs Henry J. Bakst, J. A. Foley and M. E. Lamb (Gonorrheal Septicemia and Erythema Nodosum, *Ann Int Med* **9**:790, 1935).

2 (a) Landouzy, L. Érythème noueux et septicémies à bacilles de Koch, *Bull Acad de med, Paris* **70** 400, 1913. (b) Arena, A. A. Existence du *Mycobacterium tuberculosis* dans les nodules de l'érythème noueux, *Compt rend Soc de biol* **115** 340, 1934. (c) Gutman, R. A. Un cas de érythème noueux avec présence de bacilles de Koch dans le sang circulant, *Paris med* **21** 416, 1917.

3 (a) Brian, O. Untersuchungen über die Aetiologie des Erythema nodosum, *Deutsches Arch f klin Med* **104** 272, 1911. (b) Hildebrandt, W. Zur Aetiologie des Erythema nodosum, *Munchen med Wchnschr* **54** 310, 1907.

4 Ernberg, H. Erythema nodosum and Tuberculosis, *Am J Dis Child* **46**:1297 (Dec) 1933, *Erythema Nodosum*, *Nord med tidskr* **4** 230, 1932.

5 Wallgren, A. Paratuberkulose Krankheitserscheinungen, in Engel, S., and von Pirquet, C. *Handbuch der Kindertuberkulose*, Leipzig, Georg Thieme, 1930, vol 1, p 809, *Tubercle Bacilli in Children with Erythema Nodosum*. Demonstration by Gastric Lavage, *Am J Dis Child* **41** 816 (April) 1931.

6 Dickey, L. B. Erythema Nodosum and Tuberculosis in Children, *Am Rev Tuberc* **26** 614, 1932.

7 Hess, J. H., and Berman, S. L. Erythema Nodosum in Childhood, *M Clin North America* **12** 49, 1928.

who were in contact with patients with pulmonary tuberculosis⁸ Symes⁹ has observed that in persons with erythema nodosum an acute and fatal form of tuberculosis is peculiarly liable to develop within six months Tuberculous meningitis not infrequently follows an attack of erythema nodosum¹⁰

3 Careful follow-up studies over a period of years have shown that in an unusually high percentage of patients with erythema nodosum tuberculosis subsequently develops This is especially emphasized by Scandinavian workers¹¹

4 In several instances erythema nodosum has appeared in epidemic form in families and among school children after exposure to infectious pulmonary tuberculosis¹²

5 It has been observed that a high percentage of patients with erythema nodosum show a negative reaction to tuberculin¹³ before the eruption but that the reaction often becomes positive during or shortly after the appearance of the cutaneous lesion A positive reaction to the tuberculin test in children with erythema nodosum has been considered significant Chaufford and Troisier¹⁴ injected tuberculin intradermally

8 Holmes, E M Some Aspect of Dermatological Work in Denmark, Brit J Dermat **46** 84, 1934

9 Symes, J O Significance of Erythema Nodosum, Brit J Dermat **44** 181, 1932

10 Foerster, O H The Association of Erythema Nodosum and Tuberculosis, J A M A **63** 1266 (Oct 10) 1914 Stokes, J H Erythema Nodosum and Tuberculosis Report of a Case Terminating in Tuberculous Meningitis, with Necropsy, Arch Dermat & Syph **3** 29 (Jan) 1921 Meara, F S, and Goodridge, M The Relationship Between Erythema Nodosum and Tuberculosis, with the Report of a Case, Am J M Sc **143** 393, 1912 Howe, J Duncan Erythema Nodosum and Tuberculous Meningitis, Brit M J **2** 864, 1921

11 (a) Giertsen, C Ninety-Three Cases of Erythema Nodosum, Acta med Scandinav **82** 87, 1934 (b) Ustvedt, H J, and Johannessen, A S Érythème nouveau tuberculose ultérieure, ibid **80** 262, 1933 (c) Engelsgaard, H d'U A, cited in Erythema Nodosum and Tuberculosis, Lancet **1** 597, 1931 (d) Mogenssen, E Reinvestigations in Erythema Nodosum, Acta med Scandinav **80** 480, 1933 (e) Forman, L, and Whitwell, G P B Preliminary Observations on Erythema Nodosum, Guy's Hosp Rep **84** 213, 1934 Arena^{2b}

12 Landau, A Multiple Cases of Erythema Nodosum in a Class of School Children, Arch Dis Childhood **7** 77, 1932 Rotnes, P L Eine Familien-Endemie von Erythema nodosum, Dermat Ztschr **67** 259, 1933 Brian^{3a}

13 Gamstedt, E Ueber die Tuberkulinempfindlichkeit bei Erythema nodosum vor der Eruption, Monatschr f Kinderh **59** 111, 1933 Laurinsich, A Eritema nodoso e tubercolosi, Pediatria **40** 1309, 1932 Heimbeck, J, quoted from Giertsen^{11a}

14 Chaufford, A, and Troisier, J Érythème nouveau expérimentale par injection intradermique de tuberculine, Bull et mém Soc méd d hôp de Paris **27** 7, 1909

into a patient with erythema nodosum, and nodules developed which could not be differentiated from the spontaneous nodules

Ernberg¹⁵ has stated that the histologic appearance of an excised nodule of erythema nodosum is the same as that of the nodule produced by injection of tuberculin into a patient who does not have erythema nodosum. He was able to produce an exacerbation of erythema nodosum in patients by the injection of tuberculin.

6 The blood picture of patients with erythema nodosum shows slight neutrophilic and eosinophilic leukocytosis and monocytosis, which Hoyer¹⁶ claimed resembles an anaphylactic reaction, possibly to proteins of the tubercle bacillus. Moritz and Dóra,¹⁷ studying the local blood picture of the lesions of erythema nodosum and of nodules due to the injection of tuberculin, found a preponderance of lymphocytes in both and concluded that the former lesion is due to an allergic reaction on a tuberculous basis.

7 Phlyctenular conjunctivitis is associated with tuberculosis, and Nobécourt and Ducas¹⁸ and Foiman and Whitwell^{11e} have emphasized the same association in erythema nodosum.

There is little doubt, then, that erythema nodosum may be a manifestation of tuberculosis. The association appears to be more common in children than in adults. Perhaps the reason we have observed a more frequent association with the streptococcus is that most of our patients have been adults. We have observed the same histologic appearance in the nodule resulting from injections of streptococcus nucleoprotein and tuberculin as in the nodule of erythema nodosum. Even if erythema nodosum is caused by the local activity of the tubercle bacilli, it would be unusual to find the organisms in excised nodules, since Rist and Rolland¹⁹ have shown that if tubercle bacilli are injected intradermally into tuberculous guinea-pigs and the site of the injection is excised in twenty-four hours, it is difficult to find the organisms, as they are quickly destroyed by lysis.

A study of the problem of erythema nodosum similar to ours has been made by Collis²⁰ in London. He gave cutaneous tests with the

15 Ernberg, H. Erythema nodosum. Natur und Bedeutung, *Jahrb f Kinderh* **95** 1, 1921.

16 Hoyer, W. A. Untersuchungen über das Blutbild bei Erythema nodosum mit Hinblick auf die Aetiologie, *Acta med Scandinav* **57** 587, 1923.

17 Moritz, D. U., and Dóra, A. Das lokale Blutbild bei Erythema nodosum, *Arch f Kinderh* **104** 65, 1935.

18 Nobécourt, P., and Ducas, P. Érythème noueux et conjonctivite phlycténulaire, *Presse méd* **42** 1241, 1934.

19 Rist, E., and Rolland, J. Étude sur la réinfection tuberculeuse, *Ann de méd* **2** 13, 1914.

20 Collis, W. R. F. A New Conception of the Aetiology of Erythema Nodosum, *Quart J Med* **1** 141, 1932.

nucleoprotein endotoxic fraction of *Str haemolyticus*, tuberculin and the toxin of the scarlatinal streptococcus. In this manner he found that some patients reacted to the streptococcus product and not to tuberculin, and the reverse was true in another group. He concluded that erythema nodosum is a type of hyperreactive response of the tissues to different bacterial allergens and that the allergens responsible for erythema nodosum in London are commonly tuberculin and hemolytic streptococcus endotoxin. However, more recently, Collis²¹ has stated that the streptococcic "types" of erythema nodosum are rare and that in the majority of cases in children the condition is tuberculous.

Pilot²² has observed erythema nodosum as a sequela of streptococcic sore throat. He also isolated the organism and produced typical nodules in these patients by the intradermal injection of streptococcus filtrates. Pilot and Davis²³ have seen erythema nodosum occur in patients with septic sore throat due to *Streptococcus epidemicus*. Goldstein,²⁴ Stone²⁵ and Shephard²⁶ have called attention to erythema nodosum in subjects with streptococcic sore throat. Gaub²⁷ stated that he had obtained the streptococcus from the blood stream of patients with erythema nodosum. Traut²⁸ has described a patient who showed unusual sensitivity to the streptococcus and who had repeated attacks of Henoch's purpura and erythema nodosum.

Coghievina²⁹ and Möriz³⁰ stated the opinion that erythema nodosum may be a complication of scarlet fever, while Slot³¹ claimed to have obtained good results with scarlatina serum in the treatment of erythema nodosum.

21 Collis, W R F. Erythema Nodosum. *Lancet* **2** 732, 1934.

22 Pilot, I. Focal Infection and Erythema Nodosum, *J A M A* **101** 2145 (Dec 30) 1933.

23 Pilot, I, and Davis, D J. Sporadic Septic Sore Throat, *J A M A* **97** 1691 (Dec 5) 1931.

24 Goldstein, H I. Erythema Multiforme and Erythema Nodosum with Streptococcic Sore Throat, *M J & Rec* **134** 266, 1931.

25 Stone, W R. Erythema Nodosum Associated with Streptococcic Fautis, *New York M J* **118** 673, 1923.

26 Shephard, E. Septic Sore Throat Complicated by Erythema Nodosum, *Brit M J* **1** 902, 1926.

27 Gaub, W H. Erythema Nodosum, *J A M A* **100** 601 (Feb 25) 1933.

28 Traut, E F. Hypersensitivity in Rheumatic Disease, *M Clin North America* **18** 1237, 1935.

29 Coghievina, B. Aetologie des Erythema nodosum, *Wien klin Wchnschr* **37** 413, 1924.

30 Möriz, D V. Erythema nodosum und Scharlach, *Arch f Kinderh* **103** 227, 1934.

31 Slot, G. Erythema Nodosum Treated with Antistreptococcal Serum, *Lancet* **2** 600, 1934.

Some physicians believe that erythema nodosum is a link in the rheumatic syndrome Mackenzie³² was one of the first to point this out More recently, Holmes,³³ Markson³⁴ and Claman³⁵ have observed endocarditis developing in patients with erythema nodosum

Of less importance is the theory that erythema nodosum is a specific infectious disease the etiologic agent of which is unknown Evidence in favor of this is that the disease has a definite age and seasonal incidence, it is known to occur in epidemics and the clinical course is one of an orderly sequence of events³⁶ Goldberg-Curth³⁷ stated as her belief that there is a true idiopathic and a symptomatic form of erythema nodosum She said that it may develop in the course of nearly every infectious disease and as a cutaneous reaction to toxic substances Fornara³⁸ stated that he did not think it necessary to have cutaneous lesions in the course of the disease, this being the exception rather than the rule To explain the relationship to tuberculosis, he stated that cutaneous lesions appear in persons who are hyperallergic—and this is true of tuberculous persons

Besides the tubercle bacillus, other organisms have been cultured from the lesions of erythema nodosum Rosenow³⁹ obtained an organism from several patients which he described as a diphtheroid bacillus closely resembling the streptococcus group Moon and Strauss⁴⁰ have isolated an organism varying greatly in morphology which they have named *Corynebacterium cutis-nodosae*

It is our belief that evidence is in favor of the theory that erythema nodosum is the result of a nonspecific reaction to a variety of infectious

32 Mackenzie, S On Erythema Nodosum, Especially Dealing with Its Connection with Rheumatism, Tr Clin Soc London **19** 215, 1886

33 Holmes, A H Erythema Nodosum, Lancet **2** 784 1934

34 Markson, A Antistreptococcal Serum for "Rheumatic" Affections, Brit M J **1** 129, 1935

35 Claman, I A Erythema Nodosum A Link in a Rheumatic Syndrome, Am J Dis Child **48** 1448 (Dec) 1934

36 Symes, J O Erythema Nodosum An Acute Specific Fever, Brit M J **2** 741, 1921 Comby, J Érythème noueux chez les enfants, Arch de med d'enf **26** 329, 1923 Woringer, P Érythème noueux familial, J de med de Paris **42** 241, 1923 London, A A Nodal Fever, London, Bailliere, Tindall & Cox, 1905

37 Goldberg-Curth, A Zur Pathogenese des Erythema nodosum, Monatschr f Kinderh **61** 249, 1935

38 Fornara, P Le probleme de l'érythème noueux, Rev franç de pediat **6** 723, 1930

39 Rosenow, E C The Etiology and Experimental Production of Erythema Nodosum, J Infect Dis **16** 367, 1915

40 Moon, V H, and Strauss, A Erythema Nodosum, Character and Etiology, Arch Dermat & Syph **26** 78 (July) 1932

or toxic agents. Such a point of view has been expressed by Blumer⁴¹ and Josephsen^{41a}

Pilot²² and others⁴² have observed the development of erythema nodosum in patients with lymphogranuloma venereum. Pilot produced a typical lesion of erythema nodosum in a patient with lymphogranuloma venereum by the intradermal injection of the Frei antigen.

Elwell⁴³ presented an instructive case in which several attacks of erythema nodosum and an axillary abscess were related to infection about the teeth.

Erythema nodosum has been reported as occurring in the course of chronic meningococcic septicemia,⁴⁴ in syphilis,⁴⁵ after influenza⁴⁶ and in association with ulcerative colitis.⁴⁷

The drugs that have been implicated as the cause of erythema nodosum are bromides⁴⁸ and potassium iodide.⁴⁹

CONCLUSIONS

Since a variety of toxic agents may be the cause of erythema nodosum, careful clinical observations are necessary in every case to determine the precipitating factor. It may be a manifestation of tuber-

41 Blumer, G. The Febrile Types of Erythema Multiforme and Erythema Nodosum, *New England J Med* **195** 515, 1926.

41a Josephsen, G. Erythema Nodosum, *Ugesk f læger* **95** 423, 1933.

42 Amtman, L., and Pilot, I. Lymphogranuloma Inguinale, *Arch Dermat & Syph* **26** 868 (Nov) 1932. Hellerstrom, S. A Contribution to the Knowledge of Lymphogranuloma Inguinale, *Acta dermat-venereol (supp)* **1** 5, 1929.

43 Elwell, L. B. Erythema Nodosum and Focal Infection, *Brit M J* **1** 974, 1935.

44 Montgomery, L. C. Chronic Meningococcal Septicemia, *Canad M A J* **20** 266, 1929. Master, A. M. Meningococcemia with Endocarditis, *J A M A* **96** 164 (Jan 17) 1931. Netter, A. Fièvre intermittente par septicémie meningococcique, *Bull et mem Soc med d hôp de Paris* **41** 1018, 1917. Morgan, J. H. Chronic Meningococcus Septicemia, *Bull Johns Hopkins Hosp* **32** 245, 1921.

45 Levisseur, F. J. Erythema Nodosum Syphiliticum (Mauriac's Disease), *J Cutan Dis* **29** 579, 1911. Stillians, A. W., and Seneor, F. E. Erythema Nodosum Syphiliticum, *Arch Dermat & Syph* **1** 607 (May) 1920. Fischl, F. Erythema nodosum lueticum, *Spirochätenbefund und Histologie, Arch f Dermat u Syph* **129** 361, 1921.

46 Boganovitch, V. Five Cases of Post-Influenzal Erythema Nodosum, *Arch Dis Childhood* **5** 56, 1930.

47 Brooke, P. A. Erythema Nodosum-Like Lesions in Chronic Ulcerative Colitis, *New England J Med* **209** 233, 1933. Rankin, F. W., Barger, J. A., and Buie, L. A. The Colon, Rectum and Anus, Philadelphia, W. B. Saunders Company, 1932, p. 238.

48 Weber, F. P. Erythema Nodosum with Tuberculous Bacillaemia and Meningitis, *Brit J Child Dis* **21** 119, 1924.

49 Perrin, L. Un cas d'érythème nouveau dû à l'iodure de potassium, *Marseille-med* **29** 567, 1892.

culosis It appears from the literature that this association is more common in children Streptococcic infection, especially of the upper respiratory tract in adults, often precedes the eruption In our experience this association has been more common than that of tuberculosis and erythema nodosum It may occur in patients with evidence of acute rheumatic fever Erythema nodosum sometimes appears to be related to infection about the roots of teeth There also appears to be a group of cases in which the causative agent cannot be elicited All persons with erythema nodosum should be followed carefully after recovery for evidence of tuberculosis, endocarditis or a focus of infection, for instance, around the roots of the teeth

SUMMARY

Ten patients with erythema nodosum were critically studied

No evidence of tuberculosis was present, except in one patient

The following data indicate a causal relationship between *Str haemolyticus* and erythema nodosum In five of the ten patients erythema nodosum was preceded by a sore throat, and cultures in four cases revealed *Str haemolyticus* of the beta type, intradermal injection of a streptococcus endotoxin (nucleoprotein) produced nodules similar to the lesions of erythema nodosum in eight of the ten patients, excised streptococcic nodules and the lesions of erythema nodosum revealed the same histologic appearance, similar lesions were produced by the injection of broth filtrates of streptococci isolated from two of the patients The same picture has been produced by the injection of tuberculin

An analysis of the records of one hundred and thirty-three patients treated for erythema nodosum at the Boston City Hospital from 1924 to 1934 revealed a similar causal relationship to streptococcic infections and, in addition, to rheumatic fever

A general review of the literature is presented

Erythema nodosum appears to be a nonspecific inflammatory reaction of the skin to a variety of bacterial, toxic and chemical agents

ESSENTIAL THROMBOPHILIA

REPORT OF FIVE CASES

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There are three well defined occlusive diseases of the arteries thrombo-angitis obliterans, thrombo-arteriosclerosis obliterans and occlusion due to embolism¹ In our experience 95 per cent of the cases of occlusive disease of the arteries are accounted for by these three diseases In the remaining 5 per cent are included a small number of unusual forms of obliterative arteritis, types which at present are of greater pathologic than clinical interest aneurysm with thrombosis, cervical rib with thrombosis of the peripheral artery and an irregular form, present in a small number of cases, which for lack of a better term has been designated simple thrombosis² It was recognized that the last-mentioned group of diseases probably represented a clinical entity, but until a sufficient number of cases were observed, the pathologic picture was studied and the course of the disease was followed over a period of years it would be impossible to attempt to make an intelligent classification

The following clinical description is fairly typical for this group of diseases The patient who has sudden occlusion of one of the larger arteries of the extremities is usually an active adult If thrombosis is massive and progressive, the usual signs of arterial insufficiency appear ulcers or frank gangrene In addition to the arterial lesions, the superficial or deep veins may be thrombosed The process then may become stationary, with the development of an adequate collateral circulation, or it may become progressive, and the patient may lose an extremity Other vessels may become thrombosed in addition to those in the limbs, namely, the cerebral, renal and coronary vessels Phenomena of infarc-

* Dr Brown of the Division of Medicine, the Mayo Clinic, died on Nov 28, 1935

1 Buerger, Leo The Circulatory Disturbances of the Extremities Including Gangrene, Vasomotor and Trophic Disorders, Philadelphia, W B Saunders Company, 1924

2 Brown, G E, Allen, E V, and Mahorner, H R Thrombo-Angitis Obliterans Clinical, Physiologic and Pathologic Studies, Philadelphia, W B Saunders Company, 1928

tion may occur in the kidneys, lungs and spleen. After a variable length of time and after complete subsidence of all symptoms a relapse may occur. No primary disease may be found to explain this thrombosing tendency. Neither polycythaemia vera nor any blood dyscrasia is found to be present. The pathologic changes in the vessels seem fairly characteristic and are of a bland, nonreactive form. There is usually only a slight reaction in the wall of the vessel or none. The pathologic picture does not in any respect resemble the usually recognizable type. There is no demonstrable disease in the tunics of the blood vessels, as thrombosis takes place in robust and active subjects, which rules out the slowing of the blood flow in the arteries as an etiologic factor. The major pathologic process seems to involve the stability of the suspension of the blood platelets rather than disease of the blood vessels.

The fairly characteristic clinical course in the five cases which form the basis of this report and the finding of certain variations in the coagulating properties of the plasma associated with these episodes of thrombosis led us to believe that we were dealing with an entity.

METHOD OF STUDYING THE COAGULABILITY OF THE BLOOD

The test for determining the coagulability of the blood is based on the ability of the oxalated plasma to clot on the addition of solution of calcium chloride. This is the original test of Howell, termed the prothrombin test. In two previous reports³ a standardization of this test was reported on, and its interpretation and value were discussed. It was demonstrated that this test does not determine the prothrombin value but that it is a general test for the coagulability of the blood, consequently we have termed it a test for determining the coagulability of the plasma.

After venipuncture 4.5 cc of blood is withdrawn in a cleaned and slightly oiled syringe and added to 0.5 cc of a 1 per cent solution of potassium oxalate in a test tube. The test tube is allowed to stand for a couple of hours, in order to obtain a relatively clean plasma after sufficient sedimentation of the erythrocytes has taken place. With a capillary pipet 0.2 cc is removed from this plasma layer to a Wassermann test tube, which is placed in a water bath at a constant temperature of 37.5 C. To this plasma is then added 0.2 cc of a 0.5 per cent solution of calcium chloride. This addition will start the process of coagulation. The point at which the test tube can be turned upside down without the loss of any of its contents is considered the end-point. The time between the addition of the solution of calcium chloride and the end-point, which is measured with a stop-watch, is considered the coagulation time of the plasma. The average normal coagulation time is found to be two hundred seconds. In order to obtain comparative values, we have preferred to express the results of studies of coagulability in the form of an index, which is arrived at by dividing the average coagulation time of normal plasma by that of the patient's plasma. If the coagulation time of the patient's plasma is prolonged in relation to the normal, the index will be less than 1. This is a typical finding in cases of hemophilia, in thrombo-

3 Nygaard, K. K. Coagulability of Blood Plasma, Proc Staff Meet, Mayo Clin 7 544-548 (Sept 21) 1932, Coagulability of Blood Plasma. Remarks on the Technic of Its Determination, *ibid* 9 151-156 (March 7) 1934.

cytopenic purpura and in jaundice in which there is a hemorrhagic tendency. The index will be higher than the average normal index of 1 when the coagulation time of the plasma is shortened in relation to the average normal time.

REPORT OF CASES

CASE 1—A man aged 27 of Scandinavian descent was admitted to the clinic on Feb 18, 1932. He had gonorrhea in 1923 but otherwise had been in good health until four days before his admission to the clinic. For many years he had been smoking one package of cigarets daily. There was no history of rheumatic fever or of symptoms of an early stage of heart disease.

On February 14, while walking down the street in the morning on his way to work, the patient was suddenly seized with extreme pain in both legs which caused him to fall to the ground. Dry heat was applied, and his legs, which looked white and were cold, were massaged for two hours. The left leg then regained its normal color, and he was able to move it normally. The lower portion of the right leg, however, remained blanched, and there were episodes of severe pain and impairment of the motor function.

At the time of the patient's admission to the hospital he weighed 155 pounds (70.4 Kg). Ten months previously he had weighed 135 pounds (61.3 Kg). The temperature in the morning ranged from 99 to 102.8 F, and the pulse rate ranged from 90 to 120 beats per minute. The blood pressure in millimeters of mercury was 118 systolic and 78 diastolic. The boundaries of the heart were found to be within normal limits. The cardiac rate was regular, and the tones were found by auscultation to be normal.

TABLE 1—*Pulsations in Various Arteries in Case 1**

Artery	Right	Left
Brachial	4	4
Radial	2 (?)	4
Ulnar	4	4
Femoral	0+	4
Popliteal		4
Dorsalis pedis		0
Posterior tibial		0

* In the following tables 0 denotes no pulsation, and 4 denotes normal pulsation.

On examination of the lower extremities the left leg appeared normal and did not change in color on elevation or dependency. There was a yellowish-appearing dry gangrene of the entire foot, and proximal to this was an area of gangrene of the first stage which reached up to the knee on the medial side, 2 or 3 inches (from 5 to 7.6 cm) higher than on the lateral side. The pulsations in the various arteries are tabulated in table 1.

The patient looked sick and toxic. At operation, which was not performed until seven days after the patient's admission to the hospital and eleven days after the acute arterial occlusion, amputation was carried out at the junction of the middle and the lower third of the right leg. The femoral artery was found to be filled with a soft clot, which dropped out easily.

Prior to operation the patient had a moderate degree of tachycardia while in the hospital. After operation the temperature continued to vary between 99 and 101 F for one week, rising on one occasion to 102.8 F in the evening of the fourth postoperative day. After the first week the temperature subsided.

somewhat and remained lower for two or two and a half weeks. The tachycardia, however, continued after operation, the pulse rate varying between 120 and 130 beats per minute. At the end of the third week the pulse rate gradually fell to between 80 and 100 beats per minute. An electrocardiogram taken the day before operation was essentially negative. This preoperative tachycardia was explained on the basis of toxemia due to the gangrenous leg. On the fourth day after operation pain developed, and a friction rub was heard over the entire precordial region. An electrocardiogram taken the following day indicated complete bundle branch block on the left. In two days the precordial pain disappeared, while the friction rub at the base still persisted for another day or two.

The patient felt fairly well after the operation until the seventh postoperative day, when he suffered an attack of pain in the left groin. A diagnosis of thrombosis of the left femoral vein was made.

On the twenty-eighth day after operation the patient complained of sudden pain in the small of the back and in the region of the left kidney. The first specimen of urine examined contained a large number of erythrocytes and a large amount of albumin. The value for urea was 42 mg. Hematuria lasted all the time the patient stayed in the hospital, ninety-nine days after operation. For a few days following the onset of the pain in the renal region the specimens of urine contained a few granular and hyaline casts, which, however, later disappeared almost entirely. The blood urea values did not at any time show marked changes. On the forty-fourth postoperative day the phenolsulfonphthalein test indicated an excretion of only 35 per cent in two hours. The value for serum sulfates varied between 66 and 76 mg. per hundred cubic centimeters. It was evident that the patient was suffering from renal insufficiency, and appropriate treatment was given. At no time did the observation of variations in the blood pressure indicate the presence of any hypertension. Examinations of the ocular fundi revealed no abnormality.

On the thirty-seventh day after operation the patient complained of pain in the calf of the left leg. A diagnosis of thrombosis of the short saphenous vein was made. On the forty-ninth day pain developed in the region of the left elbow, with all the evidence of thrombosis of the left basilic vein. On the fifty-first postoperative day a diagnosis was made of thrombosis of the right basilic vein and thrombosis of the superficial vein of the inner portion of the left thigh. The following day pain developed in the left popliteal region, with induration and tenderness of the popliteal vein.

Three days later, on the fifty-fifth postoperative day, there was thrombosis of a superficial vein in the abdominal wall in the right lower quadrant. After the sixty-first day there was extension of the thrombotic process in the basilic veins on both sides, both in a proximal and in a distal direction. During these episodes of thrombosis there had been practically no rise in the body temperature and little if any local inflammatory reaction.

During the following two or three weeks there still were signs of small recurrent migrating regions of thrombosis in the superficial veins, especially of the arms. At this time there was a marked improvement in the patient's general condition. An investigation of the urinary tract was undertaken in order to determine the source of the hematuria. A pyelogram revealed that the right and left calices, pelves and ureters were normal. The source of the microscopic hematuria could not be ascertained. The patient left the hospital on June 1, ninety-nine days after amputation of the right leg.

The patient returned for another examination on September 1 of the same year. Although he had not been doing any work, he had been feeling well since his dismissal from the hospital. There had been no recurrence of thrombosis. The results of examination of the arteries at this time are given in table 2.

TABLE 2—*Pulsations in Various Arteries in Case 1 at the Second Examination*

Artery	Right	Left
Brachial	4	4
Ulnar	4	4
Radial	2	4
Femoral	0	4
Popliteal		4
Dorsalis pedis		2
Posterior tibial		0

TABLE 3—*Pulsations in Various Arteries in Case 1 at the Third Examination*

Artery	Right	Left
Brachial	4	4
Ulnar	4	4
Radial	2	4
Femoral	0	4
Popliteal		4
Dorsalis pedis		2
Posterior tibial		3

TABLE 4—*Coagulability of the Plasma and the Platelet Counts in Case 1*

Date	Index of Coagulability*	Platelets per Cu Mm of Blood	Comment
12/13/32			Acute occlusion of second, third and fourth fingers of left hand, thrombosis of right basilic vein
12/27/32			Admitted to clinic
12/28/32	1.4	875,000	
1/ 4/33	0.9	357,000	
1/ 9/33	0.8	352,000	
8/23/33			Second admission, large ulcer due to stasis
8/28/33	0.6	280,000	
2/ 1/34			Recurrent occlusion of first toe on left foot
3/ 5/34	1.2	475,000	
9/28/34			Occlusion of fourth finger of left hand
10/ 3/34			Occlusion of first toe of each foot
10/ 4/34	1.4	325,000	
10/ 9/34	1.1	419,000	
10/19/34	0.9	355,000	
10/26/34	0.9	350,000	
10/30/34			Fourth finger of left hand and first toe of each foot amputated
11/16/34	1.2	312,500	
11/10/34	0.8	365,000	

* The average index value for normal subjects is 1.

On April 28, 1933, the patient returned for a third examination. There were no complaints. There had been no recurrence of thrombosis. Results of the examination of the pulsation of the arteries at this time are given in table 3. This examination indicated definite improvement in the circulation of the left leg.

At this time there was persistent hematuria. A combined intravenous phenol-sulfonphthalein test revealed a return in two hours of 65 per cent. The general examination otherwise did not reveal anything of significance.

A letter was received from the patient's sister stating that he had died on March 1, 1934, at a hospital in the South, where he had gone to spend the winter. It was later found that he died of pulmonary embolism.

Comment—One thing is obvious in this case—the condition is to be classified as belonging to the group of organic obliterative diseases of the arteries. Arteriosclerosis is ruled out because of the age of the patient, the clinical examination and the microscopic examination of the arteries from the amputated leg (fig 1), which did not reveal degenerative changes in the arterial wall. The patient belonged to the age group characteristic of thrombo-angitis obliterans. Against a diagnosis of thrombo-angitis obliterans, however, was the patient's



Fig 1 (case 1)—Part of the right femoral artery, showing little cellular reaction in the media and adventitia. The thrombus occluding the vessel is of the bland, nonorganized type.

history before the onset of the disease. There was nothing in this history to indicate that he had ever had any subjective or objective symptoms of arterial insufficiency before the acute onset of the disease. There had been no signs of superficial phlebitis. Microscopic examination of the resected vein (fig 2) did not show the inflammatory changes characteristic of lesions of the veins in thrombo-angitis obliterans. The most difficult problem in this case was the question of the nature of the acute occlusion of the femoral artery. One could assume that an embolus or thrombus in the bifurcation of the iliac arteries struck without warning at the time of the acute onset, and it is possible also that

the temporary absence of pulsation in the arteries of the left leg was due to spasm. At the time of the patient's admission to the hospital it was difficult to see how the heart could have been the source of the embolus, so far as could be made out at that time no demonstrable pathologic change was present in the heart, and the previous history did not indicate any trace of the presence of a cardiac lesion. The onset of acute pericarditis four days after amputation, with persistent tachycardia before as well as three weeks after amputation, suggested the presence of some obscure cardiac lesion. One suggestion was localized myocardial infarction, with mural thrombosis and subsequent pericarditis over

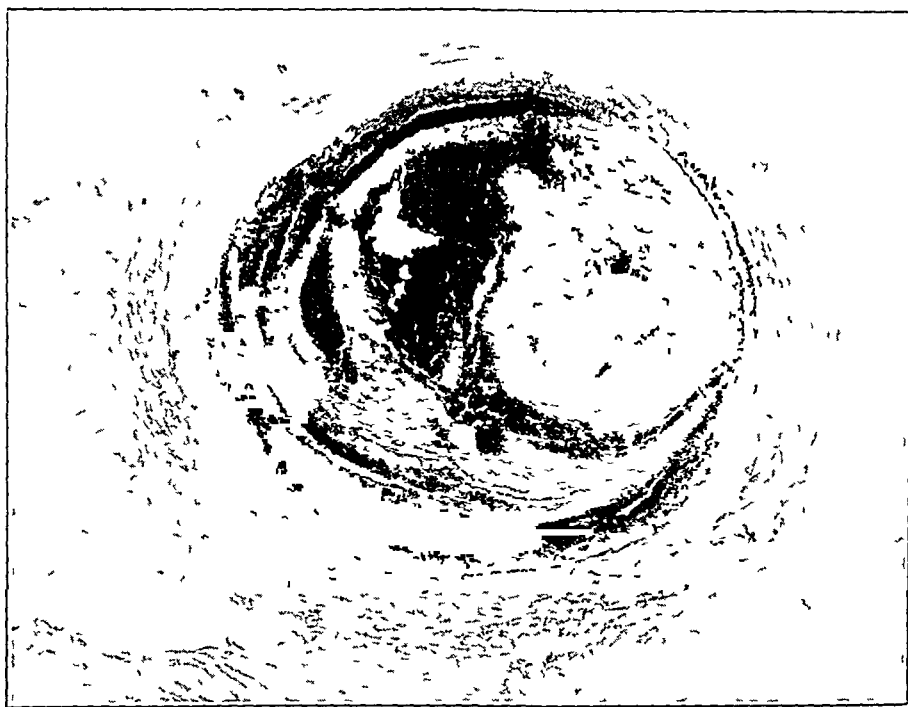


Fig 2 (case 1) —A thrombosed superficial vein from the abdominal wall

this lesion. This, however, is purely a conjecture and a dubious one, because of the absence of any subjective cardiac symptoms before the acute arterial occlusion of the leg.

At the time of the patient's admission to the hospital the embolic nature of the occlusion was questioned, for the reason that the pain which he suffered did not seem to be of the extremely severe nature seen in typical cases of acute embolic arterial occlusion. Therefore the possibility was discussed that the patient might have had a thrombus form in situ, which had led to acute arterial occlusion. It is difficult to believe that in a large artery, with no injury to the wall of the vessel and a rapid flow of blood, there is much chance for a thrombus to form, and we readily admit that such a hypothesis in this case must be advanced with reservations. Irrespective of the stand one takes as to

the cause of the original occlusion, one is impressed with the fact that there was a marked tendency toward thrombosis of the veins in this case, which was evidenced by the development of seven active stages of thrombosis in addition to several small migrating regions of thrombosis in the veins. This patient, therefore, appeared to have had a tendency toward thrombosis, and microscopic study of a specimen removed from the thrombosed vein for biopsy did not disclose an inflammatory condition that could be thought to be responsible for such a tendency.

These clinical and pathologic investigations were supplemented by studies of the protein content of the serum and of the coagulability of the blood plasma (fig 3). The figure indicates that while the patient

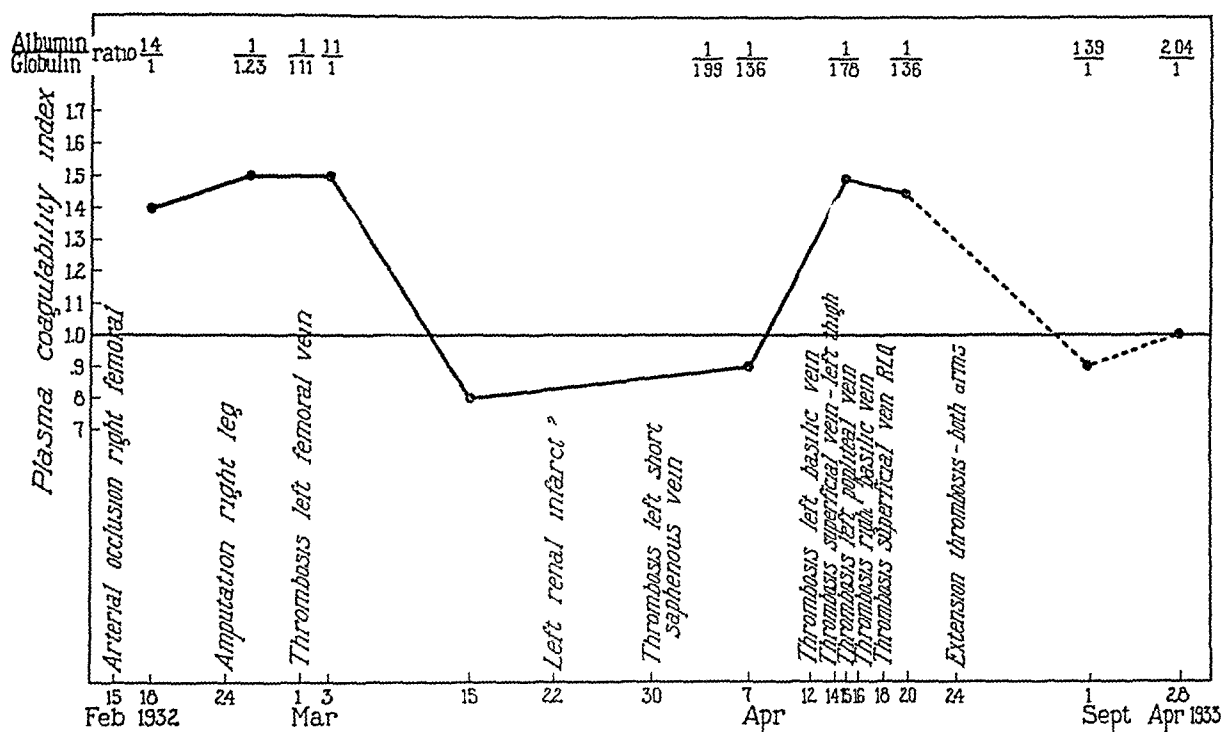


Fig 3 (case 1) —Graph showing the variability of the plasma coagulability during thrombosing episodes

remained in the hospital there were two periods during which there was demonstrated a high degree of coagulability of the blood plasma and that the active phases of the formation of thrombi fairly accurately coincided with these two periods of a high degree of coagulability. Searching for a more definite quantitative change in the blood, it was found, as is indicated by the figure, that after the first day in the hospital the patient had an almost constant inverse albumin-globulin ratio. The distribution of the serum proteins was in favor of the less stable proteins, mainly the globulin-fibrinogen fraction. It is too early to debate the etiology and the consequences of these quantitative and qualitative changes in the blood. The impression, however, remains that

this was a case in which the most outstanding clinical picture was one of vascular thrombosis in microscopically normal vessels and, further, that this was a case in which changes in the coagulability of the blood plasma and in the distribution of the serum proteins seemed to coincide with periods of active thrombus formation

CASE 2—A hardware merchant aged 49, of English and Scotch descent, was first admitted to the clinic in February 1925. He had been in the habit of smoking three or four cigars a day. At the age of 21 he contracted gonorrhea, which was complicated by swelling, pain and stiffness of both knees and ankles of seven weeks' duration. Four years later he had recurrence of the pain, redness and swelling of both knees and of the joints of both feet. After that he had repeated attacks of arthritis. The diagnosis at this time was chronic infectious arthritis of both knees, both ankles and the metatarsophalangeal joints.

The patient returned to the clinic in December 1932. In September of that year he had slight pain in the calf of the left leg for a few days. In the latter part of October he was seized with severe pain in the left flank, followed after a short while by frequent and urgent urination, with passage of bloody urine, and by frequent stools. Gross hematuria lasted for three days and then cleared up gradually and never returned. On November 8 the patient noted pain and swelling of the third finger of the right hand, associated with swelling of the back of the hand. The finger was cold. This condition lasted for about a week.

On December 13 the patient noticed that the index and second and third fingers of the left had were bluish, they later turned white, and a high swelling developed on the dorsum of the left hand. This swelling gradually disappeared, and the fingers regained their normal color in the course of a week. The skin, however, turned black over an area the size of a half-dollar, situated on the dorsum of the second metacarpophalangeal joint. This incident was accompanied with severe chilling sensations on the first day, but fever was not present. At the same time the patient noted the onset of tenderness along the right basilic vein, which extended up to the right shoulder, with some redness along the vein.

On admission to the hospital in December 1932 the patient weighed 160 pounds (72.6 Kg), as compared with his normal weight, 173 pounds (78.5 Kg). He felt fairly well. The blood pressure in millimeters of mercury was 130 systolic and 70 diastolic, the pulse rate was 80 beats per minute, and the temperature was 98 F.

On physical examination there was no detectable pathologic change in the lungs or heart. The extremities gave evidence of the same arthritic changes as on the first examination in 1925. In addition, there was a necrotic area of skin over the base of the left index finger. There was also subsiding thrombosis of the right basilic vein. All the palpable vessels were found to be open. Examination of the eyes showed normal fields, with the media clear. The fundus of the right eye was normal, in the left eye there was resolving thrombosis of the central veins and artery, especially the temporal branches.

The blood was normal. Cultures did not yield any bacterial growth after forty-eight hours. Flocculation tests gave negative results. Roentgenograms of the left forearm and hand were negative. A simple roentgenogram of the kidneys, ureters and bladder did not reveal any shadows indicative of stone in the urinary tract. After a few days in the hospital, with local treatment of the necrotic area of the skin of the left hand, the patient went home.

The patient returned on Aug 23, 1933. The condition of his hands had gradually improved. One morning in February he noticed pain in the left calf. The next day some brownish black blisters appeared over the anterior medial surface of the left leg above the ankle and resulted in the formation of an ulcer, which persisted up to the time of his third admission to the clinic. During each day swelling developed around the left ankle, extending up to the knee, but he continued his work and was on his feet every day. No definite varicosities of the veins could be seen, except one small one above the left knee. A diagnosis was made of ulcer due to stasis secondary to thrombophlebitis. The patient was put to bed, and the edematous fluid was drained off by elevation of the limb. A skin graft was performed on September 11. After this the wound healed nicely, and the patient was dismissed on October 2.

In December 1933 the patient suddenly noted severe pain and cyanosis in the first toe of the left foot. The pain lasted for four or five hours, and then the condition cleared up completely. On Feb 1, 1934, a sudden pain was noted in the same toe, but it cleared up in two days.

The patient returned to the clinic on March 5. All the arteries of the extremities pulsated normally. The fundus of the right eye appeared normal, in the left eye it was evident that collateral circulation had been established following thrombosis of the central retinal vein. The inferior temporal vein had remained occluded, together with the accompanying artery. There was some scarring along the superior temporal vein and artery, and a small residual hemorrhage was seen posteriorly, in the macular region.

Aside from these findings, physical examination at this time did not reveal anything different from what had been found at the previous examinations. The coagulability of the plasma and the number of platelets indicated conditions within normal limits. After a short period of hospitalization the patient was dismissed with a sponge compression over the ulcerated area and a heavy rubber bandage.

His general condition after leaving the clinic apparently was satisfactory until September 1934, when there was sudden and rather severe pain and coldness in the fourth finger of the left hand, followed by a bluish discoloration that gradually involved the whole finger and nail. Marked swelling of the entire hand also occurred. On November 3 the nail on the fourth finger came off, there was a gradual development of gangrene, and blebs formed on the finger, with sloughing of the skin, leaving a denuded finger. A few days after this episode of acute occlusion in the hand the patient's feet felt cold, and he felt a hot burning pain in both large toes. These toes were completely blue and somewhat swollen. The patient reentered the clinic a few hours later. He had had at different times during the previous nine months three or four similar episodes, without any resultant ulceration.

On examination at this time the patient was found to be afebrile, a condition in which he remained throughout his stay in the hospital. The blood pressure was normal. Physical examination showed that the heart was normal. The entire fourth finger of the left hand was in a stage of dry gangrene (fig 4A). Large bluish blisters covered most of each big toe (fig 4B), which appeared to be in a stage of gangrene. The feet felt very warm to the touch, whereas the toes felt only moderately warm. All the palpable arteries in the feet and hands were open.

The leukocytes numbered 5,300 per cubic millimeter of blood. The differential count was normal. The total serum protein content was 4.71 Gm per hundred cubic centimeters, the albumin fraction 1.8 Gm, giving an albumin-globulin

ratio of 1:16. Flocculation tests were negative. The first specimen of urine revealed a few erythrocytes and pus cells (grade 3). The hematuria remained unchanged during the patient's stay in the hospital. Studies of the plasma on his first day in the hospital showed a platelet count of 325,000 per cubic millimeter, with an index of coagulability of 1.3.

The general condition of the patient was good. There was no systemic reaction or toxemia, and there was almost complete absence of pain. On October 26 amputation of both big toes and the fourth finger of the left hand was performed under local anesthesia.

Comment—The patient had had chronic infectious arthritis, which was completely inactive, leaving residual impairment of the joints. With this exception he was in excellent health. The question arises whether this arthritis could stand in any causal relationship to the recurrent episodes of thrombosis. The evidence is against this, however, first, because disease of the blood vessels is not observed in the course of

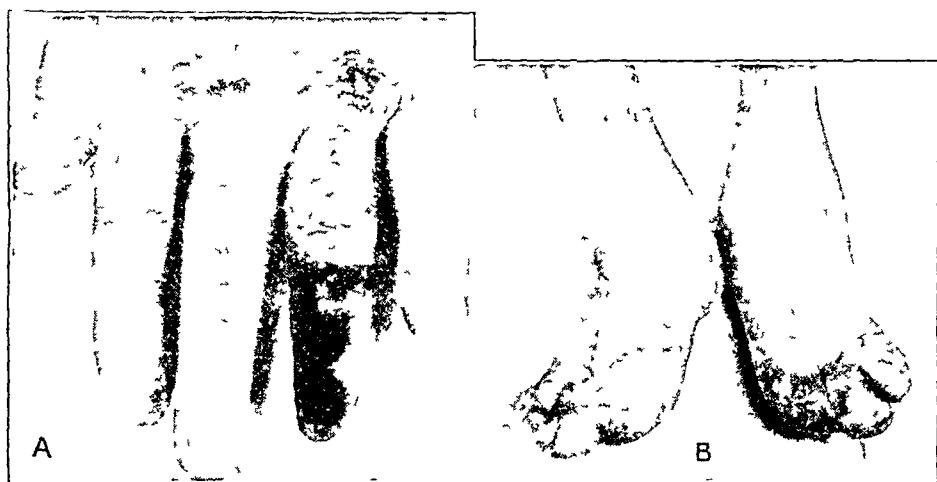


Fig 4 (case 2)—*A* shows the left hand and *B*, the feet at the time of the patient's admission to the clinic.

arthritis, and, second, because too long an interval elapsed between the active period of arthritis and the onset of the thrombosing disease. The absence of clinical evidence of arteriosclerosis, supported by the fact that degenerative changes were not observed in the involved vessels, excluded arteriosclerosis as the etiologic factor in this case.

In about 5 per cent of cases of thrombo-angitis obliterans occlusion of the digital arteries is observed, with normal pulsation of the arteries of the wrist and foot. Against the diagnosis of thrombo-angitis obliterans in this case, therefore, was the widespread nature of the thromboses, the process including the retinal arteries and veins, and the nonreactive nature of the phlebitis and the arteritis, as observed clinically. The microscopic picture of the vascular lesions of the digital arteries and veins did not resemble in any respect the inflammatory changes seen in cases of thrombo-angitis obliterans.

The nondemonstration of any source of an embolus, the long period of observation and the identical situation of thrombi in the consecutive episodes of occlusion do not favor the diagnosis of a condition of embolic origin. The pertinent facts in this case were episodes of arterial and venous thrombosis involving the left short saphenous vein, the arteries of the fingers and toes, the right basilic vein and the central retinal artery and vein and possibly renal infarction also. The impression is strong that this process was on the basis of a recurring thrombosis not attributable to disease of the blood vessels.

As will be seen in table 4, studies of the coagulability of the plasma and the platelets gave evidence of a moderately increased coagulability on two occasions, namely, fifteen days after the episode of arterial occlusion and thrombosis of the vein in December 1932 and on the day after occlusion of the arteries of both great toes (Oct 3, 1934). Only during the first episode was a high platelet count encountered. In table 4 is given also the date of the episodes of thrombosis. These studies reveal some correlation between the episodes of thrombosis and the changes in the coagulating properties of the plasma. There was a cyclic behavior in the coagulability of the plasma, periods of rapid coagulation being followed by a return to normal or to subnormal levels.

CASE 3—A barber, an American Jew aged 47, was admitted to the clinic on Aug 29, 1932. For several years he had been a heavy smoker (from twenty to forty-five cigarettes a day). Until 1928 he had enjoyed excellent health, from that time, however, his feet and legs had begun to tire easily when he walked around in the barber shop. At no time, however, had he suffered pain or claudication, and he had not had superficial phlebitis. This tiredness of his legs and feet had progressed slowly. In 1930 his toes had become red and had burned and pained, usually at night. These sensations had been partially relieved by immersion of the feet in cold water. Relief had not been obtained on elevation of the feet. Various kinds of weather had not affected these sensations.

In November 1931 the patient accidentally injured the small toe of the left foot, sustaining an abrasion, which had not healed. His local physician diagnosed the condition as thrombo-angitis obliterans. After five injections of typhoid vaccine the ulcer on the toe healed. On April 23 the patient was suddenly taken ill with severe abdominal cramps associated with fever, nausea and vomiting. This condition lasted for eight hours, whereupon the patient was taken to a local hospital, where an exploratory operation was performed. He was then informed that he had acute pancreatitis and that the capsule of the pancreas had been split. The postoperative course was uneventful, and the patient was dismissed in good condition. His feet, however, continued to bother him. About Aug 1, 1932, a small blister developed on the small toe of the right foot, followed by a nonhealing superficial ulcer. A dependent position of the foot had given the most relief.

When the patient was admitted to the clinic his temperature was 98.8 F, and he remained afebrile during his stay in the hospital. The pulse rate and the blood pressure were normal. The fourth toe of the left foot was in a pre-gangrenous stage, and there was also a superficial pre-gangrenous area at the

base of the small toe of the right foot. There was mild rubor of the toes on dependency and mild blanching on elevation. There were no clinical signs of arteriosclerosis. All the palpable arteries were pulsating. Examination of the eyes and fundi revealed an essentially normal condition. Neurologic examination gave essentially negative results.

The most significant finding in this case, besides the condition of the toes, was a sharp increase in the platelet count and in the volume and coagulability of the plasma. The hemoglobin content of the blood was 15.2 Gm per hundred cubic centimeters, the erythrocytes numbered 4,520,000 and the leukocytes 17,800 per cubic millimeter. The reticulocytes amounted to 1 per cent, the differential count was essentially normal, and examination of blood smears revealed leukocytes that had undergone moderate toxic changes. The platelet count was 2,480,000 per cubic millimeter on Aug 31, 1932, and at the same time the platelet volume was 221 per cent, as compared to a normal value of approximately 0.4 per cent, according to the Van Allen method. This determination was repeated the next day for purposes of establishing a control, an average of two observations showing a platelet count of 2,450,000. Urinalysis revealed no abnormality. The index of coagulability of the plasma was 1.5.

Amputation of the fourth toe of the left foot was advised, but the patient refused operation. After a few days of medical treatment he was dismissed and advised to continue treatment at home. We were in communication with his local physician for two years, and the last we heard was that the patient was doing well and was working every day.

Comment—The original diagnosis in this case was thrombo-angitis obliterans. There were normal pulsations in the usually palpable arteries. The marked thrombocytosis and disturbance in coagulability, however, necessitated further consideration, as these changes have never been observed in a large series of cases of thrombo-angitis obliterans and arteriosclerosis obliterans. The clinical symptoms and signs in this case, when viewed critically, were not entirely characteristic of those of thrombo-angitis obliterans. The prethrombotic symptom of fatigue of the feet when standing was not that of claudication, nor was the burning distress of the feet, with an increase in the local temperature, a symptom of thrombo-angitis obliterans.

There were several episodes of thrombosis of the digital arteries of the feet during a period of nine months. There was no evidence of phlebitis, and the major arteries did not become occluded within two years. The provisional diagnosis of thrombo-angitis obliterans of an irregular type therefore was made. Embolism could be ruled out on the basis of the findings and subsequent course. As the platelet count was enormously high and there was an increase in the coagulability of the blood plasma, however, considering that there are similar clinical and hematologic findings in other irregular types of arterial occlusive disease, it seems warranted to include this case in the group of cases of thrombosing disease, in spite of the fact that it was not possible to study the involved arteries microscopically.

It is unfortunate that we have not had an opportunity to examine this patient again and have not been able to obtain information concerning the present condition of his blood. Such an examination would show whether the thrombocytosis found at the time of his visit to the clinic in 1932 was still persisting. There is the possibility that this patient had that rare form of leukemia called thrombocythemia, in which only the thrombocytopoietic apparatus undergoes proliferative changes, leading to an enormous outpouring of thrombocytes. If this was the case, the arterial disease should be considered as secondary to the disease of the blood. Without wishing to stress this part of the discussion, however, it seems reasonable to consider the problem from a different angle. In April 1932 the patient had an attack of severe abdominal pain, for which an emergency operation was undertaken the same day. The surgical diagnosis was that of acute pancreatitis. In August of the same year, when he was examined at the clinic, the thrombocyte count was so high as to lead one to believe that splenectomy had been performed, an assumption which, of course, was not in accord with the facts. The question then remained whether the patient did not suffer from "functional splenectomy." In other words, had thrombosis of the splenic artery or vein taken place at the time of the onset of the acute abdominal disease, and if so had this thrombosis extended also into the arteries of part of the pancreas, thereby cutting off part of its blood supply and consequently resulting in acute pancreatitis?

These of course are only conjectures which will remain unanswered. In a consideration of the whole clinical picture of this disease, however, such possibilities are of more than pure academic interest. They open up the way for the assumption that in this case the acute pancreatitis and the pregangrenous condition of the toes may be regarded as of the same pathogenesis as the arterial occlusion. The pancreatitis and condition of the toes will consequently have to be considered as two clinically different, but pathogenically identical, pictures of the same disease.

CASE 4—A rural mail carrier aged 53, a gentle, was in good health until February 1932, when while trying to close a garage door he felt sudden numbness and severe pain in his left hand. This hand turned white and felt paralyzed. In the course of two weeks the color of the hand returned to normal.

In January 1933, while the patient was walking, the left foot suddenly became weak and cold, with severe pain and numbness. After approximately twenty-four hours the foot regained its normal appearance. For about six months, however, there was persistent though moderate pain in the left big toe, especially on walking. On April 15, while resting, the patient suddenly became extremely dizzy and immediately afterward vomited. With assistance he was able to walk to his bed, where he stayed for eight weeks. Any attempt at sitting up in the first six weeks was followed by dizziness and by a tendency to fall to one side. After the acute attack he had diplopia and dimness of vision and for some time had difficulty in swallowing. He was not able to sneeze or cough. These con-

ditions, however, gradually cleared up. For one month after the onset he was insensitive to heat and cold over the right side of the body and over the left side of the face. After eight weeks in bed he got up and gradually recovered.

In the latter part of June 1933, three weeks before his admission to the clinic, the patient was walking a few steps when his right foot suddenly became numb and turned white and cold. Gangrene of the right foot developed. At no time was there intermittent claudication, superficial phlebitis or ulcer formation in the extremities.

On admission to the clinic on July 20, 1933, the patient was found to be in good general condition, he had no fever, and his blood pressure was normal. He remained afebrile the three days he stayed in the hospital before an operation was performed. The left eye was held slightly closed, although there appeared to be no actual ptosis. The pupils were equal and reacted to light and in accommodation. There was a marked hoarseness owing to fixation of the left vocal cord. There was dry gangrene of the entire right foot. The left foot showed a moderate degree of pallor on elevation and a slight degree of rubor on dependency. A

TABLE 5—*Pulsations in Arteries in Case 4*

Artery	Right	Left
Brachial	4	0
Radial	4	0
Ulnar	4	0
Femoral	4	4
Popliteal	0	4
Posterior tibial	0	0
Dorsalis pedis	0	0

TABLE 6—*Coagulability of the Blood in Case 4*

Date	Index of Coagulability	Platelets, per Cu Mm	Platelet Volume, Cc per 100 Cc of Blood
7/21/33	17	380,000	0.43
7/26/33	17	337,500	0.40
8/7/33	14	415,000	0.45

similar postural change in color was found to be present in the left hand, indicating an insufficiency in the arterial blood supply, the extension of which was easily determined by examining pulsations of the palpable arteries (table 5).

The routine laboratory examinations did not reveal anything of essential importance. The total serum protein content was 6.1 Gm per hundred cubic centimeters, with an albumin-globulin ratio of 1.44:1. The index of coagulability of the plasma on the day of the patient's admission to the clinic was found to be 17, as compared with the average normal index of 1, indicating a marked increase in the coagulability of the blood. The platelet count was normal (380,000 per cubic millimeter), with a platelet volume within the normal range (0.43 cc per hundred cubic centimeters of blood). A study of the coagulability of the blood during the patient's stay in the hospital is given in table 6. An electrocardiographic tracing indicated a normal condition of the conductive system of the heart.

After the patient had been in the hospital for three days, amputation of the extremity through the lower part of the right femur was performed. The postoperative course was uneventful, and the patient was dismissed on the

fifteenth day after amputation. Letters from his local physician indicate that he is doing satisfactorily. There has been no further episode of arterial occlusion.

Microscopic examination of the occluded artery removed at the time of operation revealed some interesting features, as may be seen in figure 5 *A* and *B*. The absence of degenerative processes in this artery argues against a diagnosis of arterial occlusion as the basis of a local process of arteriosclerosis. This artery was occluded by a nonorganized thrombus, and the arterial wall showed no inflammatory reaction. There was no periarterial inflammation. We must conclude from the microscopic observation that this process was different from thrombo-angitis obliterans or from arteriosclerosis.

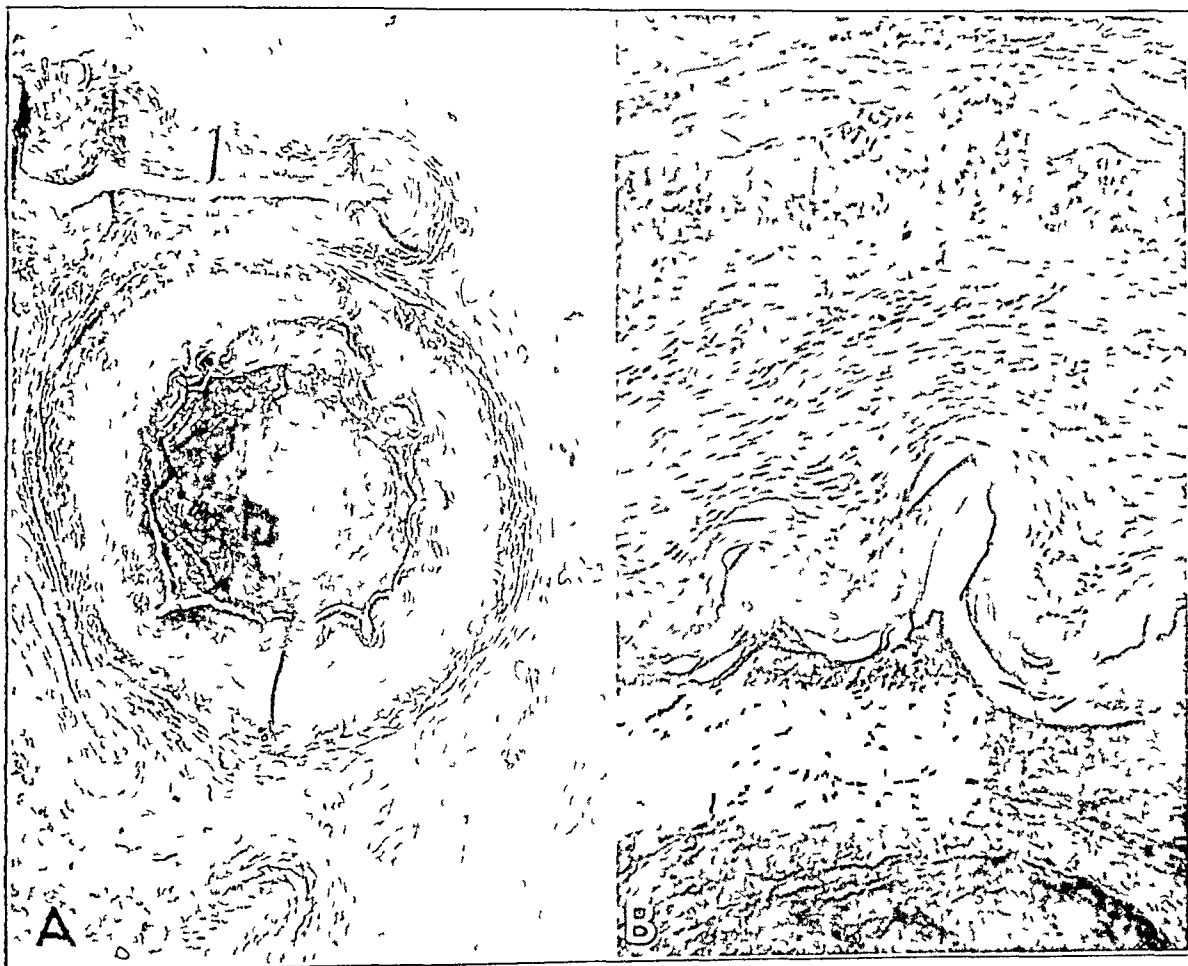


Fig 5 (case 4) —The main artery from the amputated right leg. The vessel is completely occluded by a cellular nonorganized clot. There is no cellular reaction in the vessel, except for slight infiltration of the adventitia. *A*, $\times 15$, *B*, $\times 65$.

Comment —There can be but little doubt as to the diagnosis in this case. Within eighteen months the patient had four acute arterial occlusions, the first one involving the arteries of the left hand, the second involving the arteries of the left foot, a third involving an artery of the central nervous system (left inferior cerebellar artery?) and a fourth involving the arteries of the right foot, which led to gangrene necessitating amputation.

As to the clinical diagnosis in this case, again the condition is one of the irregular forms of obliterative disease of the arteries. The patient belonged to the "early arteriosclerotic" age group. Clinical examination, however, did not reveal any signs of general distribution of arteriosclerosis. Microscopic study of the involved artery did not reveal any arteriosclerotic disease. It seems justifiable, therefore, to consider the arterial occlusive disease in this case as not being on the basis of arteriosclerosis, nor does it come under the head of thrombo-angitis obliterans, for several reasons. Superficial phlebitis had never occurred, and there was no history of subjective symptoms of insufficiency of the arterial blood supply, such as intermittent claudication, changes in color or ulceration, before the episodes of arterial occlusion. Acute thrombo-angitis obliterans may show a similar course, but in this case no other arteries were found to be involved save the ones acutely occluded. In addition, involvement of an artery of the central nervous system, such as occurred in this case, argues against a diagnosis of thrombo-angitis obliterans. The strongest argument against such a diagnosis, however, is afforded by the microscopic picture of the involved artery, which is definitely not that of thrombo-angitis obliterans.

The sudden character of the occlusion would be more likely to signify embolism. The source of a possible embolus, however, could not be traced. The patient had never had any subjective symptoms of insufficiency or other cardiac symptoms, and an objective examination did not reveal any symptoms which indicated the presence of a cardiac lesion. An electrocardiogram excluded abnormalities in the conductive system.

In this case we are again left with the impression that we are dealing with a condition of an irregular type, irregular in the respect that it does not fit into any of the groups of arterial occlusion which by clinical and pathologic experience we have learned to distinguish. By this process of elimination, therefore, and strongly supported by the positive findings of a marked increase in the coagulability of the blood, we were led to the conclusion that this may be considered among the cases of thrombosing disease.

CASE 5—A 40 year old woman of English descent was admitted to the clinic on Sept 30, 1924. She had enjoyed good health up until the time of her marriage at the age of 21. She had two living children and had had three pairs of twins, all of whom had been stillborn after from five to eight months of intra-uterine life. After the patient's last infant was born, seven years prior to her admission to the clinic, she had thrombosis of the left femoral vein. Four years later she suddenly felt dizzy and had to be helped to a chair. From there she fell to the floor in a state of semiconsciousness. For several days there were similar attacks. She noticed that her left arm and leg were paralyzed. She was brought home and put to bed, where she stayed for two weeks. After this time she began to sit up but was unable to walk around. During the year preceding her admission to the clinic she was able to walk with crutches. Since the onset of

hemiplegia there had been little improvement. In February 1924, seven months before her admission to the clinic, the patient awakened one night with severe pain in the right shoulder, elbow and hand. The whole arm prickled, as if it were asleep, and for several hours appeared white. A week before her admission to the clinic she had a similar attack. The right hand was white for four hours, and there was severe pain in the whole arm, associated with numbness, this had persisted more or less ever since.

The main reason the patient was referred to the clinic was that the local physician suspected she had a tumor of the brain. Two weeks before her admission to the clinic she awakened from a sound sleep at 2 a. m. with a severe pain in the top of the head. For a week this headache kept her awake day and night, and she finally had to be given morphine.

On admission to the clinic the patient was afebrile. The action of the heart was rhythmic, and the rate was 88 beats per minute. The right pupil was a little larger than the left, which was slightly irregular. The reflexes were normal. The right fundus was not seen because of a capsular remnant of an apparently traumatic cataract of childhood. In the left eye the disk and macula appeared normal. The vessels appeared essentially normal. The heart, lungs and abdominal organs appeared normal in all respects on physical examination. Neurologic examination revealed the classic symptoms of left hemiplegia.

The right arm and hand appeared colder than the left. A blood pressure reading for the left arm indicated a systolic pressure of 118 and a diastolic pressure of 70, whereas no reading was obtained for the right arm. The brachial, ulnar and radial arteries of the right arm were not palpable. The arteries of the lower extremities were pulsating normally, and there were no signs of arteriosclerosis of the vessels. The mobility of the right arm was normal.

Flocculation tests were negative, as were also examinations of the spinal fluid. The value for hemoglobin was 9.2 Gm. per hundred cubic centimeters, and the erythrocytes numbered 3,640,000 and the leukocytes 11,700 per cubic millimeter of blood.

The severe headache and the objective and subjective symptoms in the right arm were not clearly understood. Further developments, however, cleared up the diagnostic difficulties. The patient had been in the hospital for six days when she had severe pain in the entire right arm. The hand turned white, with streaks of cyanosis. The finger-nails were blue. The lower half of the right forearm and the hand felt cold, whereas the rest of the arm felt warm. Examination of the capillaries of the nail folds the next morning revealed almost complete stasis in all the loops. It was apparent that the main artery to the right arm had become occluded high up in the arm. There was rapidly developing gangrene of this extremity.

The patient's general condition was poor and the prognosis grave. After considerable deliberation, amputation in the mid-upper portion of the arm was decided on, this was done with the area under local anesthesia seven days after the onset of acute occlusion. The patient died seventeen days after admission to the hospital and twelve days after the onset of acute arterial occlusion.

Postmortem examination revealed the following data. The heart weighed 337 Gm. The cardiac muscle was reddish brown and of firm consistency. No valvular vegetation or mural thrombi were present. The lower lobe of the right lung was congested, otherwise there was no demonstrable lesion in this lung. There was considerable congestion in the lower lobe of the left lung, in this portion, extending from the surface about 2 cm. into the lung, was an area 4 cm. in diameter which was firm and dark reddish blue. There was also a small

scar on the pleural surface, which on section revealed an old infarction 4 by 3 cm in diameter. The pulmonary arteries were open and contained no thrombi. The pulmonary veins, however, were occluded by thrombi. Examination of the right subclavian artery revealed an organized thrombus, which began at the opening of the subclavian artery into the aorta and extended throughout the vessel as far as it can be followed and also up into the right carotid artery. The thrombus was red and contracted and almost filled the lumen of the vessel. It was adherent throughout. The left femoral veins revealed an ancient thrombotic process. The postmortem observations were otherwise essentially negative.

Comment—This patient at the time of her admission to the clinic presented a puzzling picture. Further clinical developments and the postmortem examination cleared up some of these difficulties. Even then, however, some questions remained unanswered. One thing was obvious, during the last seven years of her life, whenever she was sick, the patient had some associated lesion of the blood vessels. There was a clearcut history of puerperal thrombosis of the femoral vein, again, four years afterward, left hemiplegia developed, without obvious explanation. Three years after this the patient suffered repeated attacks of arterial occlusion. These events suggested the manifestations of a primary clinical entity. The patient's sister was said to have died of apoplexy while young. The patient had had repeated stillbirths. There was nothing, however, in the clinical and laboratory examinations which could give the faintest support for the suspicion that she had a syphilitic infection. She was comparatively young, the blood pressure was normal and there was no clinical or pathologic evidence of renal disease or arteriosclerosis. Her sex, the absence of superficial phlebitis and of a history of intermittent claudication, the cerebral involvement and finally the presence of normally pulsating arteries, except the arteries acutely involved, together with the noninflammatory character of the pathologic lesion (fig 6A and B), all argued against a diagnosis of thromboangitis obliterans. The unusual forms of arteritis were ruled out by the pathologic appearance of the vessels.

Are the acute vascular episodes to be explained on the basis of the embolism? An embolus in an artery in the internal capsule is a reasonable assumption. Embolism would mean the formation of a thrombus somewhere in the arteries of the general circulation, in the left portion of the heart or in the pulmonary veins. Clinical examination, however, showed that the patient's heart was normal, and postmortem examination did not indicate the presence of any pathologic process which logically could have led secondarily to mural thrombosis. Still the hemiplegia may have been caused by an embolus of unknown origin, or it may have been due to thrombosis *in situ* in the internal capsule. The same two possibilities are met in regard to the episodes of acute occlusion of the arteries of the right arm. It is logical to assume that the last two episodes were the result of a process superimposed on the one

which caused the first symptoms of occlusion in February 1924. This final occlusion came on without previous symptoms and with the suddenness of embolism. If there was embolism and not thrombosis, it is doubtful that the heart gave rise to the embolus, for the reasons just mentioned. At the time of postmortem examination thrombosis was found to have taken place in the pulmonary veins, and this may easily have given rise to an embolus which partly blocked the subclavian and carotid arteries, with subsequent complete blockage of the circulation to the distal part of the right arm.

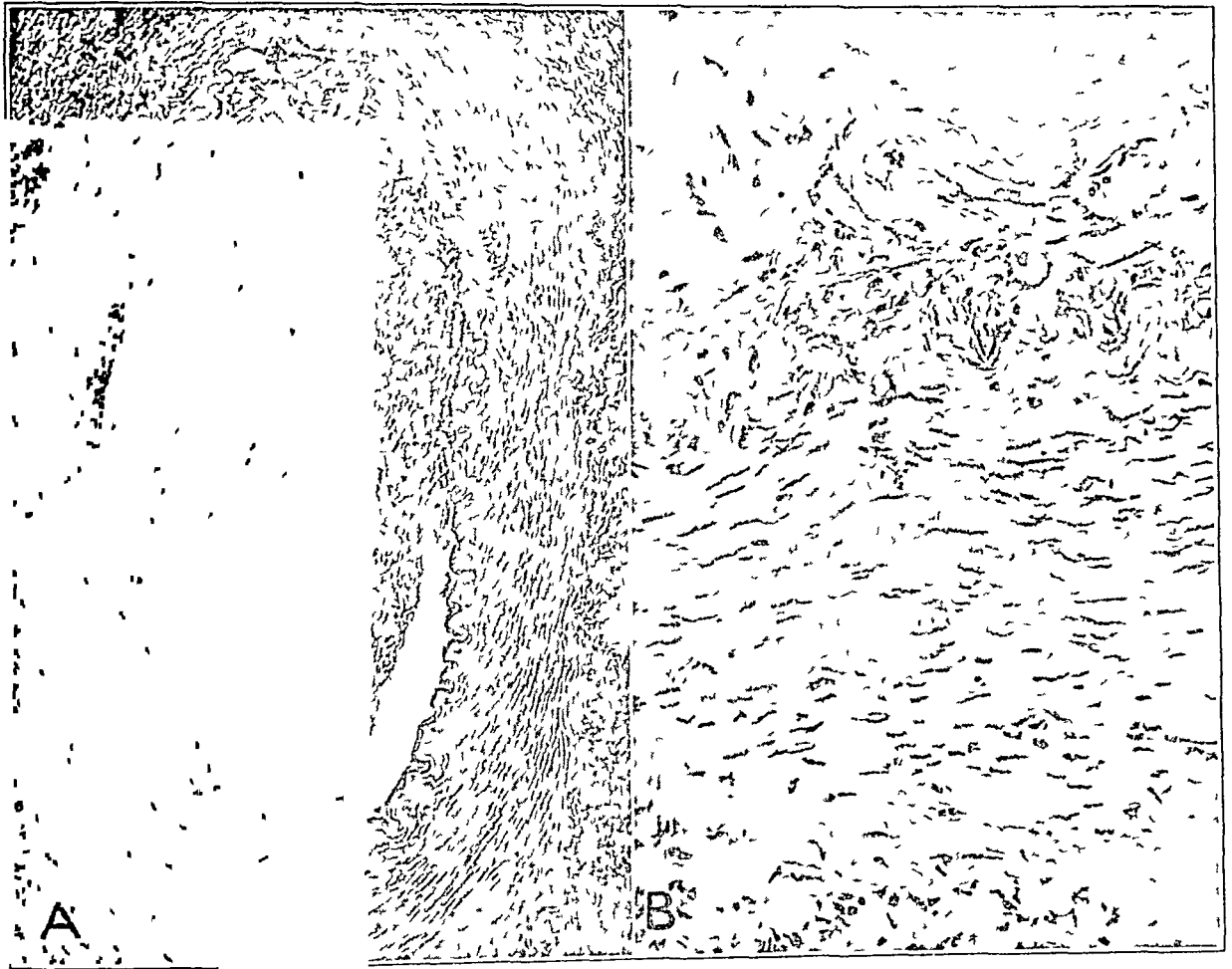


Fig 6 (case 5)—An occluded artery from the right arm, showing a slight cellular reaction in the media and adventitia. The occluding thrombus is non-organized. A, $\times 50$, B, $\times 185$.

At necropsy no accurate microscopic studies were made of the pulmonary veins. We are therefore at a loss in tracing the character of the thrombus and its possible age as well as possible lesions of the vessel wall. We admit freely that this constitutes the weak point in the presentation of this case. The pulmonary veins may have been the seat of lesions causing secondary thrombosis and, consequently, arterial embolism later. It is, however, somewhat difficult to understand how

this thrombosis could have been present in the pulmonary veins since the first occlusion of the arteries of the arm without giving any symptoms, and it is still harder to understand that it could have been present at the time of the onset of hemiplegia three years earlier. The possibility remains that the first arterial occlusion in the arm was due to primary thrombosis and that thrombosis then occurred independently in the pulmonary veins.

It is clear that the episodes of thrombosis occurred in the veins of the general circulation during the patient's last days. The fact that there was hemorrhagic infarction of the lower lobe of the left lung means that an embolus must have been present in the veins of the general circulation, because the foramen ovale was found to be closed. Together with the puerperal thrombosis of the femoral vein and the thrombosis of the pulmonary veins, this constitutes the third localization of venous thrombosis in one patient over a period of years. Within the same space of time episodes of acute arterial occlusion appeared, of which the one resulting in hemiplegia is most reasonably assumed to have been caused by thrombosis *in situ*.

Without a complete microscopic study of all the vessels and without positive findings of changes in the coagulability of the blood, we have felt it warranted to include this case in the group of cases of thrombosing disease because of the similarities in the clinical pictures. In addition, the pathologic picture did not suggest the typical picture of the known forms of arteritis or degenerative lesions of the arteries.

GENERAL COMMENT

Five cases of occlusive arterial disease which resulted in gangrene have been reported. Four of the patients (cases 1 to 4) were seen at the clinic in the last two or three years, and the fifth patient was seen at the clinic in 1924. Of a large series of cases of vascular disease studied during these years, these five cases have been regarded from the clinical point of view as irregular, in that the condition could not be considered as fulfilling the requirements of the hitherto well known groups of arterial occlusive disease either with regard to the clinical history and objective physical findings or the pathologic characteristics of the occluded vessels. These cases most likely have to be considered under the rather poorly defined term simple thrombosis. The group of conditions represented by the term simple thrombosis, however, may be said at the present to comprise so many various clinical conditions that it would be warranted, in the absence of definite knowledge as to their pathogenesis and etiology, to attempt segregation into the various groups of simple thromboses mainly on the basis of the clinical picture. In the present cases such an attempt seems all the more justifiable because of

certain characteristic features of changes in the coagulability of the plasma, a finding which also introduces the possibility for a discussion of the etiology of the pathologic process

Four of the five patients were men, and all five were gentiles, their ages ranging from 26 to 53 years. In only one of these cases could the pathologic changes be considered to be secondary to operation. In case 2 there was the characteristic picture of chronic infectious arthritis, which, however, had not been active for seven or eight years preceding the onset of the vascular disease and for this reason was not considered as an etiologic factor. In the other cases the possibility of infection was excluded. As to the presence of an underlying primary disease, none was found. In case 3 the possibility of the existence of such an underlying primary disease was not entirely excluded, as was pointed out in the discussion of the differential diagnosis, although such a possibility seems somewhat remote. We have therefore considered the process to be of a primary or essential nature.

The clinical picture is characterized by recurrent episodes of acute arterial occlusion in the large and the small arteries of the extremities as well as in those of the brain. The episodes may subside after a few hours or a few days, with complete recovery, on the other hand, occlusion may frequently lead to gangrene and to subsequent amputation of a small or large part of the involved extremity. In cases 1 to 3 the patient suffered an acute attack while going about his work and feeling perfectly well. In cases 4 and 5 the attack was just as acute, even though the patient had suffered previous occlusion of an artery of the brain. Frequently, an episode of arterial occlusion is preceded by, associated with, or followed by, one or several episodes of localized or migrating thrombosis in the superficial or deep veins. The subjective symptoms are those characteristic of any vascular occlusion, as are also the objective findings. Otherwise the general physical examination has been unimportant. The systemic reaction is characterized by low grade fever or by a completely afebrile condition, with or without leukocytosis. The other routine laboratory examinations are of no essential interest. Microscopic study of the vessels involved indicated a nondegenerating noninflammatory reaction, with slight cellular reaction in the wall of the vessel, including the adventitia, as seen in cases of simple thrombosis.

The diagnosis of the condition is reached by excluding the presence of a degenerative arterial lesion. Thrombo-angitis obliterans is ruled out mainly by the absence of persistent symptoms, subjective or objective, of arterial insufficiency before the acute onset, by the objective findings of normally open vessels, except the ones occluded after the onset, and by the absence of the chronic inflammatory character of the occlusion as seen under the microscope in the typical case of thrombo-

angitis obliterans Sterile blood cultures and the absence of inflammatory reaction exclude arteritis of specific or nonspecific origin Exclusion of the embolic factor in the occlusion is the most difficult problem in this group of cases, and it can be achieved only after the most careful physical examination The occurrence of venous thrombosis is of material assistance in the process of differentiation

Since it has seemed to us sufficiently evident that we are probably here dealing with a definite clinical entity, we have called it by a purely descriptive term, the thrombosing disease, or essential thrombophilia, and the establishment of the clinical picture has been the main purpose of this paper The clinical investigation in these cases has been accompanied with special examination of the coagulability of the plasma, according to a method previously reported One of the patients (case 5) was seen several years before such hematologic investigations were employed, and no information is at hand to indicate whether or not changes in coagulability were present In the other four cases a moderate to marked increase in the coagulability of the plasma was found In two of the cases in which the patients were followed through several episodes of the thrombosing tendency (cases 1 and 2) the active episodes of thrombosis were accompanied with coinciding episodes of increasing coagulability of the plasma The possibility that these hematologic findings were the result of hematologic reactions to the already formed thrombus has been seriously considered, however, this possibility seems justly to be ruled out by control observations in some fifty cases of arteriosclerosis obliterans and thrombo-angitis obliterans in which no such changes were observed In a large number of observations of patients who have undergone surgical operations of one kind or another similar changes of increasing coagulability of the plasma have been recorded in a high percentage of cases in which there was the complication of postoperative thrombosis or embolism These observations led to the assumption that, so far as can be seen, the changes in coagulability in cases of essential thrombophilia are not to be considered as specific for this disease It is even possible, as will be discussed later, that these changes are not altogether necessary requirements for the diagnosis of essential thrombophilia In four of the cases reported, however, this change in coagulability was present

From an etiologic point of view this strongly suggests to us the probability that the thrombosing episodes stand in some etiologic relationship to the episodes of hematologic changes, as recorded by our method of investigation of the coagulability of the plasma To prevent misunderstanding and misinterpretation we wish to emphasize the point that this does not mean that thrombosis occurs because the blood clots in the vessels It has been shown and repeatedly emphasized by

Aschoff⁴ that thrombus formation in vivo is not one of coagulation of the blood but an entirely different process. Without going into a detailed discussion of the process, it may be of interest to point out a few outstanding facts as a basis for our etiologic consideration. Morphologically, one part of the thrombus is white, it is called the head of the thrombus and is the first part formed. It is made up of a characteristic network or by the formation of lamellae, consisting of only a little fibrin but a great abundance of platelets, laid down not in the stagnated but in the streaming blood of a certain velocity. The primary question then arises: How are the platelets precipitated or agglutinated to form the first nucleus of the thrombus? A discussion of this point involves important problems of a physical, colloidal and chemical nature. It may briefly be stated that the blood can be considered as a colloidal system in which are suspended the corpuscular elements of the blood. The first process in the formation of a thrombus is a loss of suspension stability of the platelets. Theoretically this may be caused by changes in the intimal lining of the vessel, in the velocity of the blood stream or in the blood platelets themselves. In our group of cases we have found a strong indication of the presence of certain hematologic changes. It is therefore only natural that this is influencing our line of thought and that we tend to consider the changes in the platelets themselves as being of primary importance. The suspension stability of the corpuscular elements of the blood is affected by the physicochemical nature of the plasma, and this interrelation of the corpuscular suspension stability and the nature of the colloidal blood plasma has been shown by Fåhræus⁵ for the red corpuscles to be due mainly to the qualitative and quantitative condition of the serum proteins. Starlinger⁶ has pointed out that an increase in the globulin-fibrinogen fraction reduces the suspension stability of the platelets and thereby favors the occurrence of thrombus formation.

We have entered into this somewhat detailed discussion in order to reach this very point, where the value and limitation of our testing of the coagulability of the plasma may most properly be discussed. In two of our cases (cases 1 and 2) is reported a marked increase in the globulin-fibrinogen fraction of the serum proteins. In case 1 this seems to have been markedly pronounced, with a return to normal on the first visit of the patient six months after his first dismissal. We have no

4 Aschoff, Ludwig. Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924.

5 Fåhræus, Robin. The Suspension Stability of the Blood, *Physiol. Rev.* 9:241-274 (April) 1929.

6 Starlinger, Wilhelm. Ueber die klinische Bedeutung des physikochemischen Zustandes der zirkulierenden Eiweisskörper des Blutes und Gewebes, *Zentralbl. f. inn. Med.* 48:418-431 (April 23) 1927.

simultaneous determinations of the suspension stability or the agglutinability of the platelets and the coagulability of the plasma, therefore, it remains to be seen whether or not impaired suspension stability and increased coagulability are two aspects of the same factor. With this question unanswered, the possibility remains that changes in the coagulability of the plasma may not be an absolute requisite for essential thrombophilia. But with the finding of an increased coagulability of the plasma in four of our cases, it is strongly suggested that the primary hematologic change in this condition is due to the physicochemical nature of the plasma. Our qualitative and quantitative determinations of the serum protein content indicate that an increased globulin-fibrinogen fraction may be responsible, that, however, can only partly explain the process, as no direct parallel between the globulin-fibrinogen fraction and the coagulability can be found. Other principles in the plasma, either of a chemical or of a physical nature, must be involved, as is also easily deduced from conditions of hemorrhagic tendency in hemophilia and obstructive jaundice in which the marked change in coagulability is not found to coincide with any qualitative or quantitative laboratory method as yet employed. For this reason it remains entirely futile to attempt to theorize as to the primary nature of the changes leading to these hematologic abnormalities in the cases reported here. For the same reason we have not found any specific treatment for the disease.

SUMMARY

Five cases are presented in detail, in all of which there was thrombosis of the larger arteries and veins, not only of the extremities but also of other regions of the body. This thrombosing disease shows a tendency toward relapse, with recurrence of thrombosis. The thrombosis is initiated without evidence of antecedent disease or of existing disease or any known predisposing factors. The pathologic changes in the vessels are those of a nonreacting type of thrombosis without evidence of disease in the intima or other coats of the vessel. There is an associated hypercoagulability of the plasma during these episodes. It is believed that this condition represents a separate disease entity, and to it has been given the name essential thrombophilia.

REVERSIBLE AUTOHEMAGGLUTINATION WITH PERIPHERAL VASCULAR SYMPTOMS

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Prior to the beginning of the twentieth century transfusion was a dangerous procedure, usually being followed by violent and often fatal reactions. In 1900 Landsteiner¹ discovered the cause for these reactions, namely, the presence in the human serum of agglutinins which when mixed with sensitive cells cause marked agglutination. These are called iso-agglutinins because of their specific action on cells from the blood of a subject of the same species and must be differentiated from hetero-agglutinins, which produce similar reactions between the bloods of subjects of different species. On the basis of these iso-agglutinins the four blood groups are distinguished.

Certain errors in determining blood groups occasionally have arisen because of pseudo-agglutination or excessive rouleaux formation (Shattock,² 1900). This condition is common in cases of acute infection and is apparently due to increased viscosity of the serum. Marked rouleaux formation may cause clumping which simulates true agglutination. Slight dilution (1:3) dissipates pseudo-agglutination, so that it can be readily distinguished from iso-agglutination, which usually has a high titer.

Another source of error sometimes observed in grouping bloods is that due to cold agglutinins, which are so called because of their action only at low temperatures. The action is nonspecific, in that the serum will agglutinate the cells from blood of all groups and even the patient's own blood. A certain amount of confusion has arisen in the literature because of the names used to designate the phenomenon of cold agglutination: auto-agglutination, autohemagglutination and panagglutination. All these terms have also been used at one time or another to describe rouleaux formation.

From the Department of Medicine, Indiana University Hospitals, Dr. James O. Ritchey, head of department.

1 Landsteiner, K. Zur Kenntnis der antifermentativen, lytischen und agglutinierenden Wirkungen des Blutserums und der Lymphe, *Centralbl. f. Bakt. (Abt. 1)* **27**: 357 (March) 1900.

2 Shattock, S. G. Chromocyte Clumping in Acute Pneumonia and Certain Other Diseases and the Significance of the Buffy Coat in the Shed Blood, *J. Path. & Bact.* **6**: 303, 1900.

Cold agglutination, although probably observed by earlier workers, was first clearly described by Landsteiner³ in 1903, who noted its occurrence in animals. Many other descriptions of cold agglutinins in animals may be found. Table 1 differentiates types of agglutination.⁴

Christy⁵ reported the frequent occurrence of agglutination in trypanosomiasis in man. Details, however, are lacking to establish the true nature of this agglutination.

The first definite cases of cold agglutination noted in human beings were those reported by Clough and Richter⁶ in 1918. In 1931 Boxwell and Bigger⁷ were able to collect reports of only twenty-two cases which satisfied their definition. "Autohemagglutination is a clumping of the erythrocytes into irregular masses, visible to the naked eye, occurring in the presence of the subject's own serum, without bacterial action, at air temperature and reversible at body temperature." The instances

TABLE 1—*Differentiation of Pseudo-Agglutination, Cold Agglutination and Iso-Agglutination (After Landsteiner⁴)*

	Pseudo Agglutination	Cold and Auto Agglutination	Iso Agglutination
Absorption of active principle	Not absorbable	Absorbable	Absorbable
Effect of temperature on tests	Not weaker, rather stronger at 37 C than at lower temperatures	Occurs as a rule only at low temperatures	Little affected by changes of temperature from 0 to 37 C
Effect of dilution	Inactivated by slight dilution	Stands considerable dilution	Stands considerable dilution
Specificity	Nonspecific	As a rule non specific	Group specific

which satisfied this definition were noted under a variety of conditions, eight being in females and fourteen in males. Five of the subjects were in normal health, and five suffered from diverse conditions, such as bronchopneumonia, secondary anemia, pernicious anemia, hypersensitivity and unspecified anemia. In the remaining twelve cases there was some interference with the function of the liver, as shown by jaundice and enlargement of the liver. In eight cases the spleen also was reported

3 Landsteiner, K. Ueber Beziehungen zwischen dem Blutserum und den Korperzellen, *Munchen med Wchnschr* **50** 1812 (Oct 20) 1903

4 This table is adapted from that of Landsteiner cited by A. S. Wiener (Blood Groups and Blood Transfusion, Springfield, Ill., Charles C. Thomas, Publisher, 1935)

5 Christy, C. Sleeping Sickness (Trypanosomiasis), *Brit M J* **2** 1456 (Nov 26) 1904

6 Clough, M. C., and Richter, I. M. A Study of an Autoagglutinin Occurring in a Human Serum, *Bull Johns Hopkins Hosp* **29** 86 (April) 1918

7 Boxwell, W., and Bigger, J. W. Autohemagglutination, *J Path & Bact* **34** 407 (July) 1931

to be enlarged. In eleven of the twenty-two cases anemia was a definite feature of the illness. Four of the patients had syphilis. Three instances of familial occurrence were noted.

In addition to the cases reported by Boxwell and Bigger we have been able to find reports of twenty-four cases in which the authors said they considered that auto-agglutination was manifest. Only fifteen of these reports presented sufficient data so that the condition may be considered as true autohemagglutination.

Cases which cannot be accepted as instances of true autohemagglutination were reported by Reimann,⁸ Foord⁹ (4 cases), Thiudet and Ribère,¹⁰ Benhamou and Nouchy¹¹ and Foord and Randall¹². The patients reported on by Reimann, Foord and Foord and Randall all had multiple myelomas with hyperproteinemia. All of these obviously were cases of pseudo-agglutination. Benhamou and Nouchy's case cannot be considered as one of true autohemagglutination, as the serum was shown not to contain any abnormal agglutinins, rather the cells agglutinated when mixed with serum of another subject of the same blood group (Thomsen phenomenon?). The agglutination persisted at 37 C but disappeared at from 40 to 45 C. Thiudet and Ribère's case probably was one of pseudo-agglutination, as the reaction was not reversible at a temperature of 56 C for one-half hour and agglutination was not noted on dilution.

To the list of cases of true autohemagglutination we wish to add a case from the Indiana University Medical Center which is interesting in that all the symptoms can be explained by the agglutinative phenomenon. Despite a thorough search for a possible etiologic factor, none could be found, and after treatment marked symptomatic improvement was noted.

C S, a white man aged 57 years, was admitted to the medical service of the Indiana University Hospitals on Nov 6, 1935, complaining of bluish dis-

8 Reimann, H A. Hyperproteinemia as a Cause of Autohemagglutination. Observations in a Case of Myeloma, *J A M A* **99** 1411 (Oct 22) 1932.

9 Foord, A G. Hyperproteinemia, Autohemagglutination, Renal Insufficiency and Abnormal Bleeding in Multiple Myeloma, *Ann Int Med* **8** 1071 (March) 1935.

10 Thiudet and Ribère. Grande auto-agglutination des hematies, *Compt rend Soc de biol* **116** 1389 (June 28) 1934.

11 Benhamou, E, and Nouchy, A. Grande auto-agglutination des hematies précédee et suivie de grande auto-agglutination des plaquettes, *Presse med* **41** 25 (Jan 7) 1933.

12 Foord, A G, and Randall, L. Hyperproteinemia, Autohemagglutination and Renal Insufficiency in Multiple Myeloma, *Am J Clin Path* **5** 532 (Nov) 1935.

TABLE 2—Cases of True Autohemagglutination*

Case	Author	Sex	Clinical Notes
1	Clough and Richter ^a	F	Bronchopneumonia
2	Clough and Richter ^a	F	Normal (daughter of patient in case 1)
3	Kluger, I J J A M A 78 1195, 1922	F	Secondary anemia, pregnancy
4	Guthrie, C G, and Huck, J G Bull Johns Hopkins Hosp 34 80, 1923	F	Normal
5	Guthrie and Huck	F	Normal (sister of patient in case 4)
6	Guthrie and Huck	M	Normal (brother of patient in cases 4 and 5)
7	Debenedetti, V Polichinico (sez med) 31 311, 1924	F	Anemia, hemolytic jaundice, with enlarged spleen
8	Cohen, H, and Jones, A R Lancet 2 853, 1924	M	Pernicious anemia, syphilis
9	Alexander and Thompson ¹⁵	M	Leukemia (myelogenous?), anemia, enlarged spleen, jaundice
10	Greppi, E Polichinico (sez med) 32 61, 1925	M	Hypertrophic infective hepatitis, anemia
11	Greppi	M	Hypertrophic infective hepatitis, anemia
12	Li Chen Pien J Immunol 11 297, 1926	M	Syphilis, cirrhosis of liver
13	Wyschegorodzewa, W D Ztschr f klin Med 104 524, 1926	M	Jaundice, liver enlarged, syphilis
14	Greppi, E Riforma med 45 1374, 1929	M	Splenomegaly hypertrophic hepatitis, anemia
15	Debenedetti, E Presse méd 37 1688, 1929	M	Hypersensitiveness (asthma, urticaria, etc)
16	Debenedetti	M	Hemolytic jaundice, enlarged spleen and liver
17	Debenedetti	F	Normal sister of patient in case 16
18	Lloyd, R B, and Chandra, S N Indian M Gaz 65 1, 1930	F	Anemia, spleen enlarged
19	d'Antona, L Rinasc med 7 184, 1930	M	Anemia of chlorotic type, hepatocholangitis
20	d'Antona	M	Splenohepatic syphilis, anemia, jaundice spleen and liver enlarged
21	d'Antona	M	Aplastic anemia, spleen and liver enlarged
22	d'Antona	M	Jaundice, spleen and liver enlarged
23	Boxwell and Bigger ⁷	F	Anemia and atypical leukemia
24	Iwai and Mei Sai ^{16a}	M	Raynaud's disease
25	Iwai and Mei Sai ^{16b}	F	Raynaud's disease
26	van der Hoeden, J, and Verbeek, A G M Nederl tijdschr v geneesk 75 4767, 1931	M	Hypertrophic hepatic cirrhosis
27	van der Hoeden and Verbeek	M	Hypertrophic hepatic cirrhosis
28	van der Hoeden and Verbeek	M	Hypertrophic hepatic cirrhosis
29	van der Hoeden and Verbeek	F	Hypertrophic hepatic cirrhosis
30	Brule, M Hillemand, P, and Bonnard Bull et mem Soc med d hôp de Paris 49 429, 1933	M	Cirrhosis of liver
31	Manheims, P J, and Brunner, E K J A M A 101 207, 1933	F	Myelogenous leukemia, anemia
32	LeGoff ¹⁷	M	Raynaud's disease
33	Gonzales Guzman, I Arch latino am de cardiol y hemat 3 25, 1932	M	Syphilitic aortitis, splenomegaly, intestinal amebiasis
34	Sherman I Am J M Sc 188 487, 1934	F	Lobar pneumonia
35	Sherman	F	Staphylococcal septicemia
36	Sherman	F	Influenzal pneumonia, diabetes mellitus
37	Roth ¹⁸	M	Paroxysmal hemoglobinuria with vasomotor symptoms
38	Belk, W P J Lab & Clin Med 21 697, 1936	F	Lobar pneumonia

* Cases 1 to 23 are reported on by Boxwell and Bigger ⁷

coloration of the fingers, hands, toes, feet, nose, ears and tip of the tongue when exposed to cold air. At times after he had been exposed to cold the urine became red.

The patient had been in excellent health until October 1932 (three years before entry), when, while on a hunting trip, he noticed a red discoloration of the urine. During the winter of 1932-1933 he noticed a recurrence of reddish urine every time he was exposed to cold weather. At that time there were no other symptoms. During warm weather the urine remained normal in appearance. The next winter (1933-1934) the urine was again red, and the patient began to have bluish or purplish discoloration of the distal portion of all the extremities and of the nose and ears when exposed. The same sort of discoloration was noted also on the tip of the tongue after he ate ice-cream. With the discoloration there was no pain or other subjective symptoms except cold, numbness and tingling of the affected part. The bluish discoloration and numbness due to exposure to cold cleared up within five minutes after the application of heat. The urine also became clear in a short time. A year before the patient's admission to the hospital (November 1934), while making a mold and working with cold sand, his fingers became cold. The index finger of the right hand and the middle finger of the left hand became numb and black. The ends of both fingers sloughed, leaving a scar.

With the recurrence of these same symptoms in the fall of 1935 the patient was referred to the hospital for study.

His occupation was that of a molder of metals, largely aluminum, and he came into contact with metallic fumes of brass and aluminum. There had been no one with a similar disorder near him or in his factory.

There were no other complaints except of poor teeth and a rupture, for which he had worn a truss for many years. The patient had always been in robust health. He had gonorrhea in 1905 but said that he had never had syphilis. He had never had malaria. There was no history of other infectious diseases, operations or accidents. He was married, and his wife and three children (aged 31, 29 and 26) were all living and well. His father died of Bright's disease at the age of 69. His mother died at the age of 53 of typhoid. Four brothers and three sisters were living and well. Two other brothers had died—one of heart disease and the other of an unknown cause. No relative had ever complained of symptoms similar to his.

The patient was somewhat obese—height, 5 feet and 7 inches (170 cm), weight, 189 pounds (86 Kg). He appeared to be in excellent health. His face was ruddy. He had several carious teeth and enlarged tonsils. The pupils were round and of equal size and reacted to light and in accommodation. Ophthalmoscopic examination revealed no abnormality. The chest was emphysematous, but the lungs were normal. The heart showed no enlargement to percussion, the rhythm was regular, the sounds were distant and a systolic murmur could be heard at the apex. The blood pressure was 135 systolic and 90 diastolic. There was an indirect inguinal hernia on the right of moderate size which was easily reduced. The liver and spleen could not be palpated. The right index finger and the left middle finger were scarred at the tip and shortened by $\frac{1}{2}$ inch (1.5 cm). The peripheral vessels showed moderate arteriosclerosis. The radial, posterior tibial and dorsalis pedis arteries had normal pulsations. There was a decrease in the ability to feel heat in the distal portions of the extremities. Cold was recognized more readily. The vibratory sense was normal. There was a mottled bluish discoloration of the feet and hands (temperature of the room, 21 C), which was replaced by mild hyperemia when heat was applied.

The admitting diagnosis was atypical Raynaud's disease, with paroxysmal hemoglobinuria, dental caries, hypertrophied tonsils and indirect inguinal hernia on the right

Several attempts to make a count of the red blood cells were unsuccessful because of marked clumping of the cells in the diluting pipets. The hemoglobin value ranged between 10.5 and 11.5 Gm. The white blood cell count at the time of the patient's admission to the hospital was 12,200. A differential count showed polymorphonuclears, 65 per cent, lymphocytes, 19 per cent, metamyelocytes, 8 per cent, band cells, 6 per cent, myelocytes, 1 per cent, basophils, 1 per cent and reticulocytes, 16 per cent. The urine was red, acid and cloudy, with a specific gravity of 1.022. Albumin was present (0.083 per cent). Blood was present as determined by the benzidine reaction. There were no red blood cells or pus cells. Subsequent examinations failed to show blood or albumin. The function of the kidneys, as determined by the phenolsulfonthalein tests, was 70 per cent for the first hour and 10 per cent for the second. The Wassermann, Kahn and Kline tests of the blood for syphilis were negative. The basal metabolic rate was normal on two occasions (minus 7 and plus 5). The examination of the spinal fluid, including a Wassermann test and a gold curve test, gave normal results. The sedimentation rate of the blood was 6 mm in one hour. The cholesterol content of the blood was 237 and 183 mg per hundred cubic centimeters, respectively, on two occasions. The van den Bergh test showed a slightly delayed reaction. There was 0.57 mg of bilirubin per hundred cubic centimeters. The icteric index was 5. The galactose tolerance test of the hepatic function revealed no abnormality. The Takata-Ara reaction was negative. Chemical analysis of the serum showed 7.4 Gm of protein, 4.2 mg of phosphorus and 10.3 mg of calcium per hundred cubic centimeters. The fragility of the red blood cells was within normal limits (initial hemolysis, 0.46, complete hemolysis, 0.32). The Donath-Landsteiner reaction showed no hemolysis on chilling.

No trypanosomes were present in blood smears or in the blood of a rat, a mouse or a guinea-pig five days after inoculation with the blood of the patient.

Roentgenograms of the chest showed mild cardiac enlargement, considerable prominence of the left auricular node and mild congestive changes in both pulmonary fields.

During the patient's stay in the hospital the temperature remained consistently below the normal line, averaging 97.6 F (36.4 C) and ranging from 96 to 99 F (35.6 to 37.2 C).

The clumping of the blood in the diluting pipets suggested autohemagglutination, so the count was again attempted with the pipets, solutions and microscope under the rays of a heat lamp at a temperature of 37 C. In this manner counts were made without difficulty. The red blood cells numbered 3,040,000 and the platelets 203,680. No great difficulty was encountered in making satisfactory blood smears at room temperature.

Ten cubic centimeters of the blood of the patient together with 1 cc of a 2.5 per cent solution of sodium citrate was centrifugated at body temperature, and the cells were washed in physiologic solution of sodium chloride. The cells were used to determine the blood type, and the blood was found to belong to group A (type II). At room temperature (25 C) the patient's serum agglutinated the cells from all four groups with equal rapidity.

Various dilutions of the serum were made, and 1 drop of a suspension of the cells which had been separated and washed was added to each dilution. Agglutination was noted grossly and microscopically to a dilution of 1:1,024 after

thirty minutes of chilling at 10 C Agglutination disappeared in all dilutions after five minutes in the incubator at 37 C At 15 C the titer was noted as 1 64, and at 27 C, as 1 8 (table 3)

An experiment was performed to determine the temperature of the skin of the feet under various conditions The temperature was measured with the thermocouple (dermothrm) with the patient in a recumbent position The temperature of the knees, calves, ankles, dorsum of each foot and toes was measured at room heat (25.6 C) A photograph taken at that time shows the normal appearance of the skin (fig A) The room temperature was then lowered to 20 C After a few minutes the changes previously described, i e, mottling, bluish discoloration, with slight numbness, began to appear and were well marked in fifteen minutes, at which time a second photograph was taken (fig B) The

TABLE 3—*Agglutination of the Patient's Cells by His Own Serum*

Titer	1 1	1 2	1 4	1 8	1 16	1 32	1 64	1 128	1 256	1 512	1 1,024
10 C	++++	++++	++++	++++	++++	++++	++++	++++	++++	+++	+
15 C	++++	++++	++++	++++	++++	++++	+++	++	0	0	0
27 C	++++	++++	++++	++	0	0	0	0	0	0	0
37 C	0	0	0	0	0	0	0	0	0	0	0

TABLE 4—*Temperatures of the Skin in Degrees Centigrade*

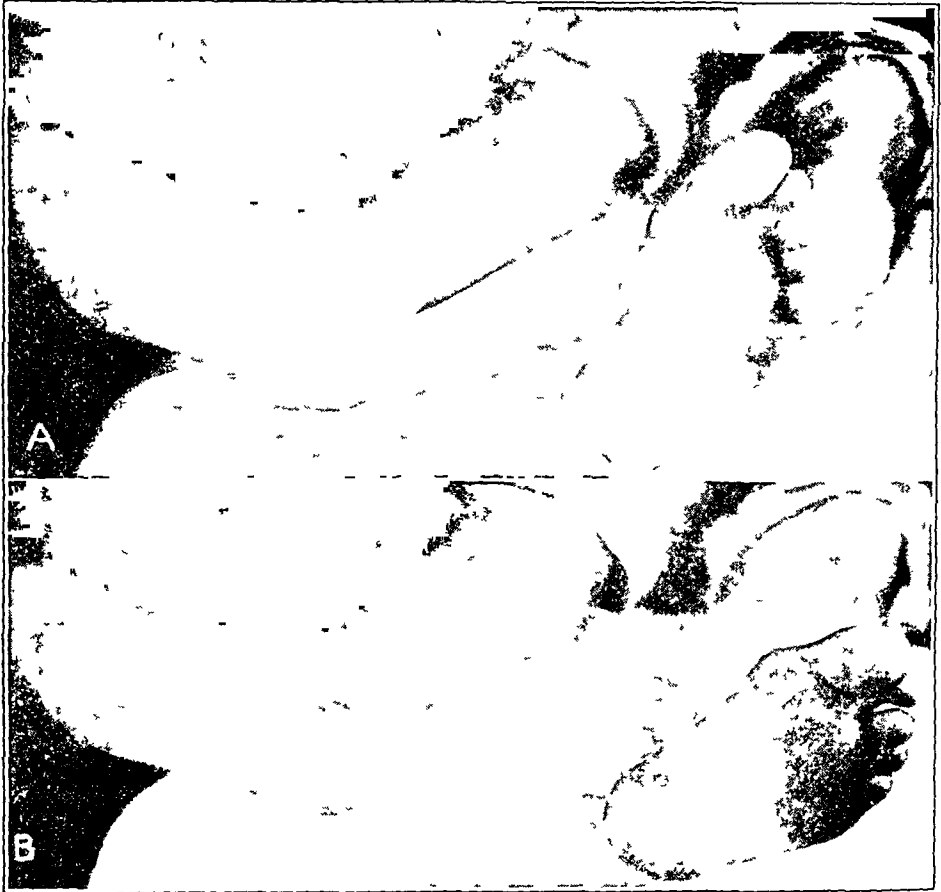
Location		Room at Temperature of 25.6 C	Room at Temperature of 20 C	After Immersion of Arms at 43.3 C for 20 Minutes
Knee	{Right	31.6	30.1	30.2
	{Left	31.3	29.8	30.1
Calf	{Right	31.4	29.9	30.1
	{Left	31.0	29.5	30.0
Ankle	{Right	29.0	26.0	25.7
	{Left	29.0	25.5	25.2
Dorsum of Foot	{Right	29.9	27.2	26.6
	{Left	29.4	26.6	26.6
Great Toe (Dorsum)	{Right	29.1	23.6	23.5
	{Left	28.0	23.0	23.2
Little Toe	{Right	26.7	22.6	22.7
	{Left	26.5	22.2	22.6

surface temperatures were again measured The patient was asked to immerse both arms to a point above the elbows in water at 43.3 C, and the temperatures were again read after twenty minutes of immersion The results are shown in table 4.

Normally, according to Landis and Gibbon,¹³ a response—an increase in the surface temperature of the foot—is noted within fifteen minutes after immersion of the forearms in water at 43 C, and in all normal subjects the temperature reaches at least 31.5 C within twenty-nine minutes Any failure to show this rise is indicative of occlusive vascular disease There was no appreciable change in the temperature in our case twenty or thirty minutes after immersion

13 Landis, E M, and Gibbon, J H, Jr Simple Method of Producing Vasodilatation in the Lower Extremities with Reference to Its Usefulness in Studies of Peripheral Vascular Disease, Arch Int Med 52 785 (Nov) 1933

On two occasions the patient was asked to expose himself dressed only in street clothes to an outdoor temperature of about 0 C. Both times he complained in about ten minutes of numbness of the hands, feet, nose and ears. Each of these members was dark purple and felt cold to touch. Room temperature restored the normal healthy color within ten minutes, the change being rapid from purple to gray to an erythematous hue (with splotchy white patches) to normal pink. Sensation returned to normal at the same time. Examination of all the specimens of urine for several hours afterward showed no trace of blood with the benzidine reaction.



A, photograph of the lower extremities at room temperature, B, fifteen minutes after the temperature was lowered to 20 C

In an attempt to produce the phenomenon by local chilling, both arms were immersed in water at 44 C for five minutes. The changes noted were not those expected, being an extreme blanching of the skin in all immersed areas and a feeling of numbness, cold and tingling. A normal color soon returned when the arms were exposed to room temperature. Specimens of urine did not contain blood.

As the moderate degree of anemia seemed to be the only finding of importance, and since many of the patients with autohemagglutination reported on in the literature had this condition, the patient was given iron (3 pills of ferrous

carbonate three times a day) and liver extract¹⁴ For empirical reasons he was also given theobromine, 15 grains (1 Gm) three times a day Under this therapy he was discharged on December 19

As he lived near the hospital, he reported from time to time that he was markedly improved and had been able to return to work He was next seen in the hospital on Feb 28, 1936, when he came in for a check-up examination At that time he stated that the symptoms noted during the past four winters had nearly disappeared, and he attributed his improvement to the therapy Blueness of the nose and ears had been noted on only three or four occasions He had been outdoors, well clothed, on one occasion when the temperature was -14°F (-25.5°C) without discomfort The return of symptoms had been noted always on raw, damp days with the temperature above freezing Hemoglobinuria was noted only twice, each time after a short exposure without proper protection on damp days The results of physical examination were essentially the same as previously Owing to the fact that he had a job to maintain, the patient stayed in the hospital only overnight His temperature at 8 p m and 8 a m was recorded as 98°F (36.6°C) Clumping of the blood in diluting pipets was again noted unless the solutions were warmed A blood count showed hemoglobin, 11 Gm, red cells, 3,120,000, and white cells, 6,700, with a normal differential count The urine was normal and showed a negative test for blood The cholesterol content of the blood was 176 mg per hundred cubic centimeters Agglutination tests again were made and showed practically no change, except that agglutination was noted to a titer of only 1:512 at icebox temperature, instead of 1:1,024

COMMENT

The significance of the laboratory and experimental work is apparent The man was in good health except for a peculiar condition of the blood, which caused some suffering and inconvenience during the winter months His financial condition and family ties made it impossible for him to move to a warmer climate The cause of autohemagglutination was not determined, although a careful search for an organic origin was made The history suggestive of paroxysmal hemoglobinuria could not be substantiated by frequent examinations of the urine for blood All the tests showed negative results except the one at the time when the patient was first admitted to the hospital The Donath-Landsteiner test for cold hemolysins also was negative

Only five cases are recorded in which the patient showed symptoms of a peripheral vascular nature (Alexander and Thompson,¹⁵ Iwai and Mei-Sai¹⁶ [two cases], LeGoff¹⁷ and Roth¹⁸) Each patient presented

¹⁴ The preparation used was extralin, 3 capsules three times a day

¹⁵ Alexander, H L, and Thompson, L D Autohemagglutination in Chronic Leukemia, *J A M A* **85** 1707 (Nov 28) 1925

¹⁶ Iwai, S, and Mei-Sai, N (a) Etiology of Raynaud's Disease Preliminary Report, *Japan M World* **5** 119 (May) 1925, (b) Etiology of Raynaud's Disease, *ibid* **6** 345 (Dec) 1926

¹⁷ LeGoff, J M Sur la forte auto-agglutinine du sang dans certaines maladies périphériques, *Presse med* **41** 628 (April 19) 1933

¹⁸ Roth, G Paroxysmal Hemoglobinuria with Vasomotor and Agglutinative Features, *Proc Staff Meet, Mayo Clin* **10** 609 (Sept 25) 1935

blueness of the peripheral parts and numbness on exposure to cold, the symptoms remitting when the parts were warmed, as in our case Iwai and Mei-Sai and LeGoff went so far as to advance the hypothesis of autohemagglutination as a cause of Raynaud's disease. LeGoff's patient showed sloughs from the lower extremities. Clough and Richter⁶ recognized the danger of intravascular agglutination, and the Japanese authors Iwai and Mei-Sai demonstrated the possibility of intracapillary agglutination in vitro, using glass tubes and passing blood through at various temperatures. They observed also what appeared to be clumping in the conjunctival capillaries after chilling by using a corneal microscope.

The theory of intravascular plugging by agglutinated cells seems perfectly plausible and would explain all the symptoms in our case. Vascular occlusion was shown to be present by testing the temperature of the skin. Since the reaction was completely and immediately reversible at internal body heat, embolic phenomena did not occur. The symptomatic improvement noted in our case without a change in climate, without any appreciable change in the blood count and without much lowering of the titer of the agglutinin might be explained by the vasodilating action of theobromine, which was sufficient to maintain adequate circulation even when agglutination did occur. Of course, spontaneous remission must be considered. Liver therapy seemed to be of little value, and this was discontinued shortly after the patient's second admission to the hospital.

The apparent confusion in the literature regarding the term autohemagglutination suggests that a more descriptive term for the condition described by Landsteiner and Boxwell and Bigger is needed. We submit that *reversible autohemagglutination* fully conveys the meaning desired and will prevent any confusion with pseudo-agglutination, iso-agglutination, panagglutination and the many other similar terms sometimes used.

In connection with this condition it is interesting to note that, in spite of the difficulty in typing and cross-matching, only one instance of an incompatible transfusion is recorded (Alexander and Thompson¹⁵). How many cases of this type have not been reported in the literature?

Dr. C. G. Culbertson, director of the laboratory of the Indiana University Hospitals, informed us that he knew of several cases in which cold agglutinins confused the technicians while typing and cross-matching the blood of donors. Unfortunately no record of these has been kept, but no difficulty in making the transfusions has been noted. The technic in our laboratory includes warming the blood to 37° C when there is any abnormality, in order to rule out cold agglutinins (reversible autohemagglutination).

It is possible that reversible autohemagglutination occurs more frequently than the literature indicates but is not observed because the test

is not made. It is also entirely possible that some atypical peripheral vascular conditions may be explained wholly or in part by the condition of reversible autohemagglutination.

SUMMARY

Autohemagglutination (cold agglutination) is differentiated from iso-agglutination and pseudo-agglutination.

A summary of the literature reveals reports of thirty-eight cases in which sufficient data are presented to confirm a diagnosis of true autohemagglutination.

The report of a case of autohemagglutination is presented in which there were symptoms of peripheral vascular disease and in which improvement followed treatment.

The theory of intravascular plugging with agglutinated cells and the production of symptoms is discussed.

The use of the term *reversible autohemagglutination* is suggested to prevent confusion in the literature.

SALMONELLA SUIPESTIFER INFECTION IN HUMAN BEINGS

REVIEW OF THE LITERATURE AND REPORT OF TWENTY-ONE
NEW CASES

A M HARVEY, M D

BAITIMORF

Since the first description of the hog cholera bacillus by Salmon and Smith in 1885, many reports of food poisoning as well as of sporadic infection in human beings due to this organism have appeared. Twenty-one patients with *Salmonella suipestifer* infection have been treated at the Johns Hopkins Hospital since April 1933. In view of the relative frequency of this infection in Baltimore, it seems desirable to report these cases and to review the literature in order to determine more clearly the clinical manifestations of *S. suipestifer* infection in man.

In 1902 Longcope published a report of two cases of human infection of a typhoid-like nature with leukopenia caused by a "paracolony" bacillus. Later studies by TenBroeck revealed that the organism isolated by Longcope belonged to the hog cholera bacillus group. Prior to the appearance of this article no infection due to this organism in human beings had been described. Many outbreaks of food poisoning caused by this bacillus have appeared in Europe and Asia, the majority of them occurring during the World War and in the following years. The literature is filled with lengthy discussions as to the pathogenicity of this organism for man. About fifty proved sporadic cases have been described. In this country three outbreaks of food poisoning and eighteen sporadic cases of the infection have occurred, eleven of the patients being admitted to the Johns Hopkins Hospital. The analysis of cases in this report includes fifty cases from the literature of proved *S. suipestifer* infection and the twenty-one cases of the present series.

DISTRIBUTION

Infection due to this organism has been reported from almost all parts of the world. Outbreaks of food poisoning have been studied in Germany, Switzerland, England, Albania, Turkey, Mesopotamia, Palestine, the West Indies and the United States. The majority of the

From the Medical Clinic of the Johns Hopkins Hospital

sporadic cases have been reported from Holland, England and the United States

EPIDEMIC OUTBREAKS DUE TO A KNOWN SOURCE OF INFECTION¹

The clinical picture is similar in all these cases. After an incubation period varying from three to ninety-four hours, but usually ranging from twelve to twenty-four hours, the patient suddenly becomes ill with headache, fever, abdominal pain, nausea, vomiting and diarrhea and in the cases of more severe involvement with prostration and even stupor. In a few instances chills occur, and some of the children affected have convulsions. In a small percentage of the cases the spleen is palpable, herpes occasionally appears, muscular weakness sometimes supervenes and, rarely, rose spots are present. Pneumonia is a rare complication, and general paresis of the muscles is described. Recovery from the acute symptoms is usually rapid, but complete convalescence may take from seven to ten days. In only five of a total of fourteen hundred and twenty-five cases in which the diagnosis was proved bacteriologically was the illness fatal. The source of infection has varied. Usually meat, such as pork, sausage or ham, is responsible, but such varied agents as tapioca pudding, ice cream, milk, crab-meat and veal have been incriminated. Knorr isolated the organisms from imported Chinese egg yolk but reported no cases of infection. In ten of the twenty epidemics the organism was isolated from the stool, in ten cases from the urine and in two from the blood stream.

SPORADIC CASES

Age, Sex, Race, Seasonal Incidence and Mortality—The majority of the cases of bacteremia due to *S. suipestifer* occurred during the first decade of life. Thirty-six of a total of sixty-seven patients, including those of the present series, belonged in this period. In striking contrast to this are the mortality statistics. In the whole series there were twenty-two deaths. Among patients less than 25 years of age the mortality was 19 per cent, while among those over this age it rose to 58 per cent. Of course the number of patients in the latter group was fairly small. The youngest patient on record was 5 weeks of age and the oldest (case 21 of this series) 70 years. Practically every race has been found to be susceptible. Among the patients reported from this hospital there were twenty-seven Negroes and only five white persons. There is no particular seasonal incidence.

¹ Bernhardt, Bosch, Clarenburg, Demnitz, Geiger, Greer and White Griffin, Gruttner, Kauffmann, Kauntz and Trawiński, Krumwiede Provost and Cooper, Lewy and Schiff, Schmidt, Schnitter, Scott, Stewart and Litterer, and Walther.

*Uncomplicated Bacteremia—Typhoid-Like Infection*²—Forty-four of the seventy-one patients were without localizing signs, eleven of the patients in the present series being of this type. In this group the average age was 13 years, the youngest patient being 7 months and the oldest 55 years of age. The sexes were equally affected, and in only nine cases, or 20 per cent, did the disease prove fatal.

The clinical picture of this type of infection is not unlike that of typhoid, and this diagnosis is often made when the patient is admitted to the hospital. However, in many instances there are features which serve to distinguish it.

The onset is usually sudden, but in from one fourth to one third of the patients the disease begins gradually over a period of two or three days. Fever is the predominant symptom at the onset. A marked degree of pyrexia is noted, the temperature often being 104 or 105 F, but this is not invariably the rule. The duration of the fever varies

TABLE 1—*The Sporadic Cases. A Comparison of Forty-Six Reported Cases with the Present Series of Twenty-One Cases*

Age, Years	Number of Reported Cases	Number of Fatal Cases Reported	Number of Cases in Present Series	Number of Fatal Cases in Present Series
0-5	17	3	10	1
5-10	5	0	4	0
10-15	3	1	0	0
15-20	6	3	1	0
20-25	3	2	0	0
25-30	5	2	0	0
30-35	3	3	3	2
35-40	1	1	2	0
Over 40	3	3	1	1
Total	46	18	21	4

considerably, but in the average case it lasts for from two to ten days. Anorexia is almost always a complaint. Vomiting and headache occur with great regularity. A shaking chill at the onset occurs in about 10 per cent of the cases. Dry cough and coryza are frequently noted. Diarrhea was complained of in thirteen of the cases, while constipation was noted in approximately 10 per cent. Worthy of mention is the frequent complaint of abdominal pain. Many of the patients have abdominal distention and tenderness and occasionally a slight degree of muscle spasm. Owing to these signs and symptoms needless operations have been performed. Other symptoms which occur occasionally are convulsions (especially in children), drowsiness, delirium, articular pains without objective findings and pain in the back. A history of epistaxis was noted in three cases.

² Bauer and McClintock, Boller, Branham, Motyca and Devine, Dijkstra, Haynes and Meiks, Hicks and Robertson, Kobe, Kruger, Kuttner and Zepp, Mackenzie, Matveld, Nabarro, White, Dyke and Scott, Neukirch, Rau and Shaw.

The physical findings are those common to any acute infection with an invasion of the blood stream. Hyperpyrexia, a coated tongue and abdominal distention are almost always present. In contrast to the findings in typhoid, the pulse rate is usually rapid. However, a relative bradycardia is occasionally seen. Meningismus is a common finding in children but is rarely observed in adults. The large majority of children are drowsy, but many of the adult patients look surprisingly alert in the presence of such a high temperature. Herpes rarely occurs. Rose spots almost never are seen. Mild bronchitis is commonly noted in older patients. In a few cases the liver is palpable, and even less frequently there is slight general enlargement of the lymph nodes. In approximately one fifth of the cases the spleen is palpable.

Complications during the course of this infection are rare. Jaundice has been reported in three cases. Two intestinal hemorrhages occurred during the course of a mild typhoid-like infection in a 28 year old Indian reported by Duncan. Although the organism obtained by culture of

TABLE 2—*The Initial Symptoms in the Twenty-One Cases in the Present Series*

Fever	21	Abdominal pain	5
Vomiting	10	Delirium	5
Cough	7	Drowsiness	4
Coryza	6	Chill	3
Diarrhea	6	Headache	2
Constipation	5	Convulsions	2
Pains in joints	2		

the blood was not entirely typical of *S. suispestifer*, serum agglutination with stock strains was 1:80, while tests with all other antigens showed negative results. Parotitis was a fatal complication in one case. Purpura occasionally developed, and its appearance was always associated with an unfavorable outcome. Culture of the urine in five of these cases gave positive results, but there were no clinical manifestations of urinary infection. In a moderate number of cases a slight degree of anemia developed during the course of the illness, but the blood returned rapidly to normal when the infection subsided. Of interest are the numerous cases in which the condition has developed in persons previously inoculated with typhoid vaccine.

In only an occasional case is the organism observed in the stool. The majority of patients present no recognizable source of the organism in the body, and the manner of its entrance and mode of dissemination are usually entirely unknown.

*Cases of Pulmonary Involvement*³—Among the pulmonary manifestations which occur during the course of *S. suispestifer* infection are

3 Bauer and McClintock, Boller, Bullowa, Kuttner and Zepp, Neukirch van der Hoeden and Hulst, and Weil and Saxl

bronchopneumonia, occasionally lobar pneumonia, pleu¹isy with effusion and empyema Twenty-four, or approximately one third of the seventy-one patients with the diagnosis proved, including the twenty-one in the present series, had definite evidence of pulmonary or pleural involvement In a large majority bronchopneumonia was noted The average age of these patients was 19 years The sexes were about equally affected Ten of the twenty-four patients died The symptoms and physical signs were similar to those seen in pneumonia due to other organisms In one of the cases reported by Kuttner and Zepp in 1933 purpura developed, and the bronchopneumonia was discovered at autopsy to be interstitial Since purpura is a common finding in pigs infected with the virus of hog cholera, the possibility of such an etiologic relationship was mentioned in this case, but no virus studies were made No other instances of pneumonia of this type have been noted in cases of *S. suispestifer* infection

The temperature is usually high, with a daily variation of from 0.5 to 2 F In the bronchopneumonic type it comes to normal by slow lysis, but several patients with essentially lobar involvement showed termination by typical crisis Frequently the pneumonia is bilateral

In six cases bacteriologic proof of the rôle played by the *suispestifer* bacillus in these infections has been obtained Five of these cases were reported in the literature, and one belonged in the present series In an unusual case of lobar pneumonia the bacillus was recovered from the sputum and from the blood stream (Bullowa) In two cases of the Glasser-Voldagsen type described by Neukirch it was obtained in pure culture from the lung at autopsy In case 18 of the present series lobar pneumonia with pleural effusion developed during the course of pregnancy, which was already complicated by myocardial insufficiency Fluid obtained by thoracentesis was sterile, but blood culture revealed a gram-negative rod, and at autopsy *S. suispestifer* was grown in pure culture from the lung Boller reported the case of a 21 year old woman in whom one week post partum a pleural effusion developed which led to empyema *S. suispestifer* was grown from the fluid The patient was entirely well four months later Van der Hoeden and Hulst obtained the organism from the pleural fluid and sputum of their patient

The combination of pneumonia and articular involvement is an interesting one Four cases of such a combination are on record⁴ Three were in infants 1, 5 and 15 months old, respectively The articular infection developed from six days to six weeks after the pneumonia had become manifest

4 Tevel, Tur and Gartoch, and van Creveld and Ruys

*Pyarthrosis and Osteomyelitis Due to S. suipestifer*⁵—In fifteen of seventy-one cases in which the diagnosis was proved by culture manifestations of involvement of the bones or joints were noted—an incidence of over 20 per cent. Only one of these cases was from the present series, but at the present time there is in this hospital a patient with *S. suipestifer* infection of the spine, a child who is not included in the present report. Seven of these patients were in the first year of life. The mortality in this group was 28 per cent. The sexes were equally affected, twelve were white, one was a Negro and one a Chinese.

The individual joints were involved as follows: knee—left in two, right in two, shoulder—left in two, right in four, ankle—left in two, right in one, and more than one joint in five cases. Two cases of osteomyelitis involving almost every bone in the body have been described (Matrossoff). One of these is included in the present series.

In the majority of these cases articular involvement was the first symptom of note. However, in several it appeared as a complication during the course of *S. suipestifer* septicemia from eight days to one month after the onset, usually being preceded by bronchopneumonia.

Case 7 of this series is of unusual interest because of the development of extensive purpura on the sixth day of illness and of osteomyelitis involving almost the entire skeleton before the fatal termination of the three month illness.

There is a period varying from a few days to several weeks before any objective evidence of articular involvement appears during which general malaise and difficulty in using the affected extremity are present. Only occasionally is a history of trauma to the joint elicited. Most of the patients have a remittent fever of varying degree, but several have been almost afebrile. On examination the involved joint is usually visibly swollen and warm. Occasionally the overlying skin is erythematous, tenderness to palpation is noted and movement is painful. Fluid is present in almost every case, and on aspiration a turbid, purulent, greenish material is obtained from which a pure culture of *S. suipestifer* is grown. Thus, the common finding is pyarthrosis. Osteomyelitis of the adjoining bone is not of infrequent occurrence.

Roentgenograms in the early stages may show nothing abnormal, but later such changes as periosteal thickening, calcification and erosion of the adjoining bone almost invariably appear. In case 7 of this series roentgenograms at first showed nothing abnormal, but, later, osteomyelitic changes were observed in almost every portion of the skeleton.

⁵ Bruin and Janssen, Dijkstra, Dijkstra and van der Hoeden, Gajzago and Gottche, Kuttner and Zepp, Langwill, Nabarro, White, Dyke and Scott, Tevel, Tur and Gartoch, Weaver and Sherwood, and Weil and Saxl.

In contrast to the cases of uncomplicated bacteremia, well marked leukocytosis was noted in five of seven cases, the count ranging from 16 000 to 28,000. In four of the fourteen patients the organism was cultured from the blood stream.

In all the fatal cases there was extensive, multiple bony involvement. No case of monarticular involvement proved fatal. In one case death occurred seven weeks after the onset of articular lesions, and at autopsy no pathologic changes could be seen.

After open drainage or repeated aspiration of the joint, together with traction or immobilization, as indicated, the temperature drops rapidly to normal, the swelling gradually subsides and in from three to six weeks free mobility usually returns. Occasionally, slight limitation of motion remains, but in many of the patients followed for from six months to two years complete function was reestablished.

In a report by Ssokoloff there were mentioned thirty cases of surgical complications. Most of these were diagnosed by agglutination reactions with stock serums of the Glasser-Voldagasen strain, similar to that found by Neukirch (1918) in his cases. The manifestations were similar clinically, roentgenographically and pathologically to those of typhoid and paratyphoid osteomyelitis.

Five cases of spondylitis, all in men between the ages of 17 and 46, were noted by Ssokoloff. The process in two began directly after the febrile illness, but in one case a latent period of three months was noted. The first patient to be seen in this country with *S. suispestifer* infection of the spine is a patient who is in this hospital at the present time.

In ten cases infection of the costal cartilage was noted, all such instances occurring in men aged from 17 to 37, in whom the latent period varied from one week to two months. In three cases multiple foci were present. Serum agglutination titers varied from 1:200 to 1:1,600, and from an abscess which developed in one case a pure culture of the gram-negative rod was obtained. In two cases fistulas developed.

Articular involvement showing a predilection for the amphiarthrosis type was noted. With the exception of a 10 year old girl, the patients were men from 17 to 37 years of age. There was always a history of preceding febrile illness, followed in from one week to two months by articular manifestations. The sacro-iliac joint was involved in four cases, the sternoclavicular joint in two, the hip joint in three, the knee joint in two and the symphysis pubis in one. Pain on active and passive motion and swelling and pain on palpation of the capsule were usually noted, and free fluid was present in the joint. In three instances the organism was cultured from the synovial fluid. Healing occurred in from five to nine months.

Aissenjeff established the causal relationship of this organism in ten cases of articular infection. The involvement was mild, as evidenced by the average duration of illness of only two weeks. The bacillus was recovered in only one case, in this case there was an abscess around the ankle joint. The remainder of the cases were proved by serum agglutination tests.

Matrosoff reported a case of multiple osteomyelitis in a 25 year old man. The series of complications appeared at intervals of from three weeks to one year after the acute infection.

Infection Complicating Surgical Procedures—Of special interest is the occurrence in this series of several cases of postoperative infection due to *S. suipestifer*. Kuttner and Zepp in 1933 reported a case of *S. suipestifer* bacteremia in which bronchopneumonia and cystitis occurred the day after a bilateral antial operation on a 28 year old Negress. Cultures of material from the sinuses and from the nose and throat were sterile, but the organism was obtained from the urine. The patient recovered. In one of Kuttner's cases, that of a 6 year old Negress with a three day history of abdominal pain, vomiting, fever, boardlike abdomen and a leukocyte count of 30,000, laparotomy was performed and the only finding was a small amount of fibrinous pus in the pelvis. After the operation the temperature remained high, and culture of the blood showed *S. suipestifer*. Hicks and Robertson described the illness of a Chinese police constable who, five days after drainage of an ischio-rectal abscess, became ill, with fever, epigastric pain, a palpable spleen and mild leukocytosis. *S. suipestifer* was cultured from the blood stream. The illness terminated fatally.

In the present series there were several cases in which a relationship to some surgical procedure was noted. In case 16, that of a 33 year old Negress, bronchopneumonia of the upper lobe of the right lung developed after laparotomy for myomas of the uterus. The organism was cultured from the blood but not from the sputum. Later an indurated area in the wound was incised, and there was a moderate amount of serosanguineous pus, from which a pure culture of *S. suipestifer* was obtained. In case 19, that of a 36 year old Negro, acute pancreatitis was noted at operation. The temperature rose to 104 F eight hours after operation, and death resulted within a few days. Unfortunately no cultures were made at the time of operation, but after death the organism was obtained from the heart blood and also from material from the peritoneal cavity. In several reported instances⁶ *S. suipestifer* has been cultured from the bile of patients with cholecystitis and of patients supposedly ill with catarrhal jaundice. Whether or not infection of the biliary tract due to *suipestifer* was present in this case before

⁶ Ssokoloff and Waldman

operation is impossible to say. Finally, in case 20, that of a 37 year old Negress with myomas of the uterus and *B. coli* cystitis, a high fever with chill developed on the second day after a cystoscopic examination. *S. supestifer* was repeatedly cultured from the blood but never from the urine. No source of infection could be found in any of these patients.

*Involvement of the Nervous System*⁷—Four fatal cases of purulent meningitis due to *S. supestifer* are on record. In one case the organism was cultured from the spinal fluid and in three cases from the meningeal pus at autopsy. Coma, convulsions, purposeless movements of the hands, cervical rigidity, hypertonicity and a positive Kernig sign were noted. All the patients were in coma on admission, and the progress to death was rapid.

Bollet reported the case of a 36 year old woman with bacteremia who on the fourth day of the illness showed signs of paralysis which he stated were like those seen in diphtheria. These gradually disappeared, and complete function returned within a few weeks.

In the Offenbach epidemic, reported on by Schnitter, many of the patients had slight disturbances of the peripheral nerves. Cervical rigidity was noted in a few. Also, transient deafness and trigeminal neuralgia occurred.

Endocarditis—Gouley and Israel observed the following unusual case. In a 4 year old white girl a febrile illness developed, with marked prostration, five days before her admission to the hospital. Forty-eight hours after her entry into the hospital consolidation developed in the upper lobe of the right lung and on the ninth day of illness a double aortic murmur was audible. The blood culture showed *S. supestifer*. The temperature returned to normal on the twelfth day of hospitalization, and the aortic murmur later disappeared. It was assumed that the patient had endocarditis due to *S. supestifer*.

As a Secondary Infecting Agent in Association with Tumor—Van der Hoeden and Hulst reported the case of a 16 year old boy who was ill for six months with enlargement of the lymph glands in the neck, widening of the mediastinum and enlargement of the spleen. The organism was cultured from material obtained by puncture of the growth, from the blood and the pleural fluid, once from the stool and regularly in the urine. The serum agglutination reached a titer of 1:12,800. At autopsy the tumor was described as an endothelioma.

Case 21 of this group is somewhat similar. *S. supestifer* bacilli were grown repeatedly from the blood of this 70 year old woman during her illness. An agglutination titer of 1:1,280 developed, and at autopsy

⁷ Kuttner and Zepp; Materna and Januschke, and Neukirch.

a secondarily infected hypernephroma was present, from which the bacillus was obtained. Cultures of the urine and stool during life were sterile.

Predominant Infection of the Urinary Tract—Although mild cystitis is not uncommon during the course of suipestifer infection, an infection of the urinary tract as the predominant feature of the clinical picture is distinctly unusual. Pyelitis has been reported (Ssokoloff). Neukirch (1918) described a case of pyelonephritis in a 26 year old man due to the Glasser-Volgadsen type of *S. suipestifer*. Ssokoloff reported a case of perinephric abscess which came to necropsy after a stormy illness of one month. A pure culture of *S. suipestifer* was grown from the pus.

THE BLOOD PICTURE

The reports in the literature are so meager in regard to the blood that chief reliance must be placed on the cases reported from this hospital. Table 3 displays the average white cell count at the time of the

TABLE 3—*Leukocyte Counts*

	Typhoid Like Picture	Pulmonary Involvement	Joint Involvement
Number of cases	19	16	8
Average	6,800	14,080	16,800
Highest	14,600	80,000	28,010
Lowest	1,700	3,800	4,900
Number above 10,000	1	6	5
Number below 5,000	6	3	1

patient's admission to the hospital in the various types of infection in our cases. It can be seen from these figures that leukocytosis is to be expected in patients with localizing signs of infection, while a normal or low count is usual in the patients with typhoid-like infection.

In contrast to cases of typhoid the development of complications during the course of suipestifer bacteremia is usually associated with marked leukocytosis. However, the white cell count in uncomplicated bacteremia tends to remain at a low level throughout the illness. In the cases among adults in which some associated disease was present the white cell count varied according to the nature of the accompanying illness.

A differential blood count has been made in so few proved cases that the following figures are of no great importance. In sixteen cases the averages were as follows: 11,800 white blood cells, 51 per cent polymorphonuclears, 41 per cent lymphocytes, 4 per cent monocytes and others 4 per cent. In eight of the cases the lymphocyte count exceeded 50 per cent. In only three instances was an increase in the number of young myeloid cells evident, and eosinophilia was reported once. The proportion of the various types of cells bears no relation to the height

of the white cell count during the course of the illness, except in the presence of an initial lymphocytosis, which disappeared rapidly in most instances at the end of the febrile period

A slight degree of anemia is a frequent finding. The average hemoglobin value at the time of admission in the present series was 75 per cent, with 4,200,000 red blood cells. In most of the cases the anemia progressed slowly during the acute stage of the illness, but after the termination of the attack the normal level was soon reached. This progression in the anemia was often observed, even when small repeated blood transfusions were being given.

BACTERIOLOGY

S. supestifer is a gram-negative motile rod which gives the sugar fermentation reactions of the paratyphoid B group but can be differentiated from this organism by its failure to ferment arabinose, trehalose and inositol (Kuttner and Zepp). Andrewes and Neave showed by absorption tests that there are two groups of *supestifer* organisms. Those of group 1 are diphasic, in that they contain two types of antigen, the specific antigen which characterizes it and the nonspecific antigen which it has in common with group 2. Group 1 is the so-called American type described by Theobald Smith, and the Western European strains are usually of the group 2 type. In the literature several strains are described by name which are culturally and serologically related closely enough to be included in the present report: (1) the American type, (2) the Kunzendorf, or Western European, type, (3) the Glasser-Voldagsen type and (4) the Oriental, or Eastern, type. All of these strains are pathogenic for animals, in which respect they differ from the closely related paratyphoid C bacillus described by Hirschfeld.

Cross-agglutination with other members of the group is so frequent that when ordinary laboratory diagnostic serums are used one may be led to a false conclusion as to the causal organism. It seems reasonable to assume that in instances in which one is not aware of the possibility of *supestifer* infection an illness due to this organism might incorrectly be diagnosed as paratyphoid fever. In case 21 of the present series paratyphoid B agglutinations were complete with the stock serums as high as 1:1,280, and only after additional sugar reactions were studied and more detailed serologic reactions were undertaken was the correct identity of the organism established.

A thorough knowledge of the serologic classification of the paratyphoid group of organisms is necessary for the exact identification of the bacterium. By absorption a type-specific serum can be produced which can serve to identify any strain by direct agglutination if a reasonable number of organisms in the type phase are present. On the

other hand, identification of a group culture will depend on the proper absorption of various type serums to remove type agglutinins for the homologous strains (Topley and Wilson)

Recognition of the possibility of cross-agglutinations together with further sugar tests will serve in most instances for the proper recognition of *S. supestifer*

Blood Culture—Blood culture is the usual method by which the diagnosis is made evident. It is fortunate that these organisms can be grown from the blood with relative ease and that bacteremia persists for a relatively long period. In fifty-three, or 74 per cent, of the seventy-

TABLE 4—Organisms of *Salmonella* Group (After Topley and Wilson)

Species or Type	O Antigens (Somatic)	H Antigens (Flagellar)	
		Type	Group
Paratyphosus B	I II	Paratyphosus B	G A
Stanley	I II	Stanley S	G A
Aertrycke	I II	Aertrycke	G A B C
Newport	IV	Newport D ₁ D ₂	G A B C
Reading	II	Reading D ₁ D ₂	G B—
Morbificans bovis	IV	Morbificans bovis	G E ₁ E ₂
Supestifer (diphase)	V	Supestifer W W ₁	G B E ₁ E ₂
Supestifer (monophasic)	V	Supestifer None	G B E ₁ E ₂
Hirschfeld	V	Hirschfeld W W ₂	G B— E ₁ E ₂
Sendai	XI	Sendai T	G E ₁
L	IX	L M ₁ M ₂	G

TABLE 5—Data on the Blood Cultures

Reported Cases			Present Series				
Day of Illness	No of Cases	No of Positive Cultures	No of Cases	No of Cultures Made	No of Positive Cultures	No of Sterile Cultures	Positive Cultures, %
1-7	28	32	7	10	8	2	80
8-14	11	12	10	13	11	2	
15-21	5	6	6	7	5	2	
22-28	1	2	3	3	1	2	33

one proved cases, including the twenty-one cases in the present series, blood culture showed positive results at some time during the course of the disease. From those cases in which the day of onset of the disease could be fairly accurately determined the figures presented in table 5 were secured.

In contrast to most infections the bacteremia which is so commonly seen in this disease persists for long periods, yet metastatic lesions are relatively infrequent. Thirty-three per cent of the cultures taken during the fourth week of the disease showed positive results.

The highest number of organisms per cubic centimeter of blood in any culture was 255. In this case the patient died. Sixty-five colonies per cubic centimeter were found in case 13 of the present series, which did not end fatally.

The Agglutination Reactions—While the presence of *S suispestifer* infection is usually proved by culture, agglutination of the serum of patients with unexplained fever has established the diagnosis in many cases. In thirty-four of the seventy-one proved cases, of which twenty-one were in the present series, a positive agglutination reaction developed. In many of the cases reported in the literature no agglutination tests were made, or they were attempted only once during the first week of the disease, so the foregoing figure is not accurate. Titers as high as 1:12,800 are found, and in case 16 of this series agglutination was strongly positive in a 1:10,240 dilution. Van der Hoeden and Hulst reported one case of pleural effusion in which the fluid obtained showed an agglutination titer of 1:400.

A rough idea of the agglutination titer during successive weeks of the disease can be obtained from table 6, which was compiled from the

TABLE 6—*Agglutination Reactions*

Week of Illness	No. of Cases	Titer						Highest Titer
		0	80	160	320	640	1,280	
1	6	1	2	1	2			
2	10	5	1	1	2	1		
3	14	1	2	2	5	1	2	1:4,000
4	9	2			4	2	2	1:4,000
5	2					1		1:4,000
6	4		1			1	1	1:5,000
7	1							1:5,000

cases of the present series and a few obtained from the literature. In the present series of cases 88 per cent of the patients showed an agglutination titer higher than 1:320 by the fourth week. In seventeen of eighteen cases positive results were obtained, and in only one was the titer less than 1:160. In the dilutions mentioned practically complete agglutination occurred.

Few figures are available concerning the duration of demonstrable agglutinins in the blood. In one case a titer of 1:250 was still present two years after the acute illness occurred. Titers of 1:500 eight months after recovery are known, and agglutination in a dilution of 1:2,000 may persist for as long as two months.

PATHOLOGY OF *S. SUIPESTIFER* INFECTIONS

There are no specific lesions which are attributable to infection by this organism. Acute splenic tumor, petechial hemorrhages in the serous membranes and cloudy swelling of the liver and kidneys are often present. Focal areas of necrosis in the liver similar to those seen in cases of typhoid are frequently present.

In the majority of cases no intestinal lesions can be discovered, and the organism cannot be grown from the intestinal contents. Involvement of the lower portion of the ileum and large intestine, with ulceration of the mucous membrane and enlargement of the mesenteric lymph nodes, has been described, but complete bacteriologic studies of the intestinal contents were not carried out in these cases, and they may have represented coexisting infection by some other organism (Neukirch, 1918).

Although the organism can often be obtained in pure culture from material from the lungs, bones and joints, kidneys, meninges and other lesions, the observations at autopsy are neither grossly nor microscopically specific for infection with *S. suipestifer*. The organism can usually be cultured from the heart blood, the spleen and elsewhere as a secondary invader in a preexisting disease state.

COMMENT

It seems reasonable to assume that infections in human beings due to *S. suipestifer* are far more common than is generally recognized. In numerous cases a diagnosis of paratyphoid fever is undoubtedly made. If in every bacteriologic laboratory the correct identification of organisms belonging to the paratyphoid B-Salmonella group were faithfully pursued the evidence of suipestifer infection would probably increase to a considerable degree.

Associated with Other Diseases—As most of the strains of *S. suipestifer* are not of great virulence, the frequent occurrence of other diseases in this group of infections is not surprising.

During the war outbreaks of this infection went hand in hand with poor nutrition, as manifested by scurvy, and severe exposure to cold and wet. The associated infection with plasmodia and the spirochete of Obermeyer is not uncommon. The organism finds fertile soil in a person whose resistance is lowered by the presence of another disease or in a young infant, whose powers of resistance are not great. Kobe reported the appearance of a subcutaneous abscess due to this bacillus in a 59 year old diabetic patient. Bosch commented on the increased incidence of the infection on the east coast of Sumatra during an epidemic of pneumonia among young children. He noted too, the frequent occurrence of combined malarial and Salmonella infection. Numerous other diseases might be mentioned which have been associated with suipestifer infection: gonococcic urethritis, arthritis, ischio-rectal abscess, peri-urethral abscess due to *B. coli*, endothelioma and bacillary dysentery.

Other diseases found in the present series are as follows: rickets, mediastinal tuberculosis, pharyngitis due to beta hemolytic streptococci, congenital heart disease, rheumatic heart disease with myocardial failure.

(a pure culture of *S. supestifer* was obtained in one case from the pericardial fluid), pregnancy, *B. coli* cystitis, myomas of the uterus and hypernephroma

Transmission from Contact and Among Members of the Same Family—Tui and Gartoch described the illness of a 1 month old child which was characterized by pneumonia and articular infection. *S. supestifer* was cultured from the stool and synovial fluid. Eighteen days after delivery the mother had a "typhoid-like infection," but no bacteriologic study was made. Suspicion of a relation of the infection in this case to the mother by transmission by means of the blood or milk was entertained but not established.

The patient reported on by Haynes and Meiks became sick during a period when the hogs on the farm were ill with cholera.

In one of Kuttner's cases the parents gave a story of a febrile illness resembling that of the patient, and the mother's serum agglutinated the organism obtained from the blood of the patient. In a second case the mother's serum agglutinated the patient's organism 1/80.

In case 6 of this series the patient had the infection in March 1935, and her cousin (case 10) had it the following May. The brother of the sixth patient was ill in the middle of May with fever, abdominal pain and headache. However, agglutination of the serum from eight members of the family proved negative. Culture of the stool from both patients was consistently sterile, and no known source was discovered.

The difference between the infection as seen in adults and that in children is striking. The incidence is higher, the course is milder and the number with articular manifestations is greater among those of the younger age group. In contrast to childhood infection, association with some usually more important disease is found with great regularity among adults.

SUMMARY

The literature on *S. supestifer* infections in human beings is reviewed, and twenty-one new cases are reported.

Epidemic outbreaks of food poisoning due to a known source of infection are common, but the infection is usually mild, and the mortality is low.

Sporadic cases occur with some frequency in Baltimore.

Uncomplicated bacteremia simulating typhoid is the most common type of infection.

In some cases the predominant feature of the clinical picture may be pneumonia, osteomyelitis, pyarthrosis, meningitis, endocarditis or severe infection of the urinary tract.

Several cases of infection complicating surgical procedures are described

It is believed that in cases of infection due to this organism a diagnosis of paratyphoid fever is sometimes made, because of the frequency with which cross-agglutinations in high dilutions with paratyphoid B antiserum occur

The organism can be grown readily from the blood stream, and the bacteremia often persists for a long time. In the present series 88 per cent of the patients had an agglutination titer of 1:320 by the fourth week of illness

Thus far no specific pathologic lesions attributable to infection by this organism have been described

In children the incidence is higher, the course is milder and the number of articular manifestations is greater

In adults there is frequently an associated disease which is of primary importance

In the majority of the sporadic cases there is no recognizable source of the organism in the body, and the manner of entrance is usually entirely unknown

The majority of cases of supestifer bacteremia occur during the first decade of life. For patients less than 25 years of age the mortality was 19 per cent, while for those over 25 it rose to 58 per cent

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TREATMENT OF ESSENTIAL HYPERTENSION WITH A DEPRESSOR SUBSTANCE PREPARED FROM THE URINE

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The treatment of essential hypertension with depressor drugs has been disappointing. The use of depressor substances that are present normally in the body, such as choline, acetylcholine, histamine, adenosine and its derivatives and guanido-acetic acid, has not been extensively investigated, owing primarily to the fact that unpleasant or toxic symptoms accompany their administration. However, there are theoretical reasons for believing that one of these substances, to which the name kallikrein has been given by its discoverers, may be of value in lowering a pathologically high blood pressure. The physiologic and chemical properties of this substance have been discussed in previous publications¹. This principle is presumably elaborated by the pancreas, it circulates in the blood stream and is eliminated in the urine, where it is present as a thermolabile colloid with certain rather distinctive biologic reactions on which its identification rests. These reactions are a fall in the blood pressure, with an increase in the amplitude of cardiac contraction, after intravenous injection into an experimental animal, and an antagonism to the pressor effect of epinephrine when injected simultaneously with it. The theoretical basis for its further trial lies in the fact that

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1 Kraut, H, Frey, E K, and Werle, E. Ueber die Inaktivierung des Kallikreins, *Ztschr f physiol Chem* **192** 1, 1930. Frey, E K, Kraut, H, and Werle, E. Ueber die Blutzuckersenkende Wirkung des Kallikreins (Padutin), *Klin Wchnschr* **11** 846 (May 14) 1932. Frey, E K. Kallikrein (Padutin) im Blut, *Munchen med Wchnschr* **80** 125 (Jan 27) 1933. Kraut, H, Frey, E K, Werle, E, and Schultz, F. Nachweis und Vorkommen des Kallikreins im Harn, *Ztschr f physiol Chem* **230** 259, 1934. Elliot, A H, and Nuzum, F R. The Pharmacologic Properties of an Insulin-Free Extract of Pancreas and the Circulatory Hormone of Frey, *J Pharmacol & Exper Therap* **43** 463, 1931. Nuzum, F R, and Elliot, A H. Insulin-Free Pancreatic Extract and the Circulatory Hormone (Kallikrein of Frey and Kraut). *California & West Med* **39** 361 (Dec) 1933.

its average concentration in the urine of a group of persons with essential hypertension was found, particularly in young subjects, to be considerably below normal² This suggested that if the concentration in the blood of this depressor principle were raised in such subjects by hypodermic injection, a decrease in the blood pressure might result, particularly if by this means a true substitution therapy had been evolved

The continental literature³ contains a number of favorable reports regarding the use of the depressor substance called kallikrein in the treatment of hypertension Frey,^a who has most forcibly called this drug to the attention of the members of the medical profession, mentioned four patients with fixed hypertension in whom the blood pressure fell for a period of from six to eleven months after a series of injections The most enthusiastic paper was that of Scharpff,^b based on the study of thirty institutional patients in whom the usual methods of therapy had been used without avail After from eight to ten injections a fall in the blood pressure occurred in all the patients, except those with malignant hypertension or contracted kidneys The author stated that he believed that this substance acts physiologically in the manner of a hormone and is the best means yet available for lowering the pathologically high blood pressure

A substance called vagotonine,⁴ a preparation made from the pancreas and probably different from the substance called kallikrein, has recently been reported as a most satisfactory drug for the treatment of hypertension

This paper is a summary of the response of the blood pressure of a group of hypertensive patients to intensive and prolonged medication with a depressor substance prepared from the urine⁵

2 Elliot, A H, and Nuzum, F R The Urinary Excretion of a Depressor Substance (Kallikrein of Frey and Kraut) in Arterial Hypertension *Endocrinology* **18** 462 (Aug) 1934

3 (a) Frey, E K Kreislaufhormon und innere Sekretion, *Munchen med Wchnschr* **76** 1951 (Nov 22) 1929 (b) Scharpff, W Die Behandlung der Hypertonie mit dem Frey-Krautschen Kreislaufhormon Padutin (Kallikrein) *Deutsche med Wchnschr* **57** 675 (April 17) 1931 (c) Leschke, E Erfahrungen mit dem Kreislaufhormon Kallikrein, *Munchen med Wchnschr* **77** 1524 (Sept 5) 1930 (d) Binswanger, H Einige Beobachtungen mit dem neuen Kreislaufmittel "Kallikrein," *Deutsche med Wchnschr* **57** 1057 (June 19) 1931 (e) A New Internal Secretion of the Pancreas foreign letter *J A M A* **95** 676 (Aug 30) 1930

4 Marklen, L, Vidacovitch, M, and Franck, C Physiologic Basis of Therapy by Vagotonine (Pancreatic Hormone), *Presse med* **41** 1745 (Nov 11) 1933

5 The preparation used was essentially the same as that which Frey described and called kallikrein

METHODS AND SUBJECTS

Methods of preparing this principle from urine have been reported in detail elsewhere⁶. The first batches were made after the method of Frey, these were crude and when given resulted in local subcutaneous reactions. Later batches became pure, and a concentration of units up to 10,000 per milligram of dried material was obtained. This substance when dissolved could be given in large doses subcutaneously without producing a local or a systemic reaction. The material was given daily or thrice weekly by intramuscular injection in doses varying from 50 to 5,000 biologic units over a period of weeks or months, to reach a total dose of from 2,300 to 64,000 units. No immediate response of the blood pressure or toxic reaction was observed. Occasionally after from six to twenty-four hours mild systemic protein reactions occurred, which, with the purer preparations now at our disposal, have been obviated.

The subjects treated were carefully chosen. Seven of them, four of whom were males, were less than 40 years of age. Four of these patients were suffering from an early stage of essential hypertension. The blood pressure in each case was occasionally within normal limits, but the frequent occurrence of fairly high systolic readings, together with a slight degree of cardiac enlargement, justified the diagnosis of hypertension. This group of patients was watched over for a long time with particular interest because the urinary output of the depressor substance was below normal and because, with the possible exception of one patient, who was suffering from mild thrombo-angitis obliterans, the disease was unaccompanied with vascular degeneration. Each of the remaining six patients, three of whom were more than 40 years of age, had a higher and more fixed blood pressure and showed some evidence of organic vascular changes.

The true evaluation of any therapeutic measure in essential hypertension is a difficult matter, and results are easily misinterpreted unless a suitable technic of investigation is scrupulously adhered to. The present study was therefore conducted in the following manner: 1 Readings of the blood pressure were made by the same observer at the same time of day for each patient. Before a reading was made the patient rested for ten minutes in a semidarkened room. 2 Control determinations were made over a period of at least ten days before the injections were started. 3 No medication other than the depressor substance was given, except for injections of colored water as a part of the control observations. 4 The total period of observation was at least fifty days, while several of the patients were followed for over a year. 5 Psychic suggestion was carefully avoided in every instance, each patient understanding that he was subjecting himself to an experimental investigation which might well prove of no benefit. For these reasons the group was necessarily small. 6 The data were discarded for any patient in whom some disturbing environmental influence, such as intercurrent illness or family worry, appeared. Enough blood pressure readings were taken during the control, treatment and follow-up periods to allow a satisfactory statistical analysis in each case.

RESULTS

In the accompanying table the mean blood pressure and the length of the control, treatment and follow-up periods, together with other pertinent data, are given for each patient. The standard deviations, as a measure of the predictable variability of the average blood pressure

⁶ Bischoff, F. and Elliot, A. H. Purification of the Depressor Colloid of Urine (Kallikrein), *J. Biol. Chem.* **109** 419 (April) 1935.

Data on the Response of the Blood Pressure to Injections of a Depressor Substance

Name	Age	Sex	Control Period			Treatment Period			Follow Up			Comments	
			No of Deter- mina- tions	Duration	Mean Blood Pressure	No of Deter- mina- tions	Duration	Total Dose, Units	Mean Blood Pressure	No of Deter- mina- tions	Duration		Mean Blood Pressure
A W	26	F	8	11 days	143 ± 1.5 84 ± 1.7	27	35 days	8,255	127 ± 1.3 76 ± 0.4				Total period of observation, 29 mo, early essential hypertension, blood pressure frequently 150 or 160 mm of mercury, two normal pregnancies during this time, previously had had two pregnancies, with hypertension and abortion
	Period 2		10	11 days	127 ± 1.6 76.5 ± 1.6	11	24 days	4,225	125 ± 0.1 76.1 ± 1.1				
	Period 3		60	5 mo	127 ± 1.1 79 ± 1	9	11 days	2,336	142 ± 4.5 92.5 ± 2				
	Period 4		21	8 mo	136 ± 1.1 80 ± 1.3	14	22 days	4,400	127 ± 2.1 83 ± 3.1	12 mo	22	138 ± 1.3 78.6 ± 1	
I S	29	M	6	12 days	144 ± 2 84 ± 1.8	33	53 days	45,250	144 ± 1.5 78 ± 1	24 mo	4	145.155 80.95	Early essential hypertension, mild Burger's disease
I W	34	M	21	16 days	175 ± 1 121 ± 2	32	48 days	64,060	173 ± 2.5 129 ± 1	24 mo	5	180.200 123.135	Cerebral hemorrhage at end of treatment period
W R	40	M	12	21 days	138 ± 3.7 98 ± 1.2	24	37 days	25,375	126 ± 1.3 86 ± 1.5	3 mo	38	126 ± 2.4 87 ± 1.4	Early essential hypertension
I K	27	M	18	30 days	152 ± 0.9 103 ± 1	11	20 days	3,700	151 ± 1.6 100 ± 1.1				
I A	23	F	10	10 days	147 ± 2 82 ± 1.5	46	5 mo	43,750	147 ± 1.2 86 ± 0.9	3 mo	4	150.155 0.40	Hypertension developed during follow up period, also had small coronary occlusion
M T	24	F	12	12 days	147 ± 2.5 88 ± 1	35	4 mo	27,100	147 ± 0.8 86 ± 1				Early essential hypertension
R T	60	F	13	12 mo	183 ± 1.1 97 ± 2.5	19	9 mo	2,400	184 ± 3.0 92 ± 1.3				Total period of observation, 6 yr onset and development of hypertension watched, finally diabetes developed (1934)
M W	43	M	10	6 mo	195 ± 1 140 ± 2.3	7	3 mo	2,370	220 ± 2.6 120 ± 3	18 mo	15	211 ± 2 135 ± 1.5	
G G	43	M	6	1 mo	205 ± 11.7 133 ± 1	75	8 mo	10,000	190 ± 1.5 125 ± 1.1				

during these periods, have been calculated. In general the results are disappointing. Only two patients (A W and W R) showed a significant fall in the mean blood pressure during or following the period of treatment. That the magnitude of the fall in these subjects was slight, even though fairly consistent, is well illustrated by chart 1 (W R). Since the blood pressure of each of the remaining patients did not change, we are inclined to attribute this result to some alteration of factors in the environment of these patients which was beyond our knowledge and control.

No appreciable amelioration of symptoms was evident in our patients as the result of the administration of the depressor substance. During the period of treatment one patient had a cerebral hemorrhage, and

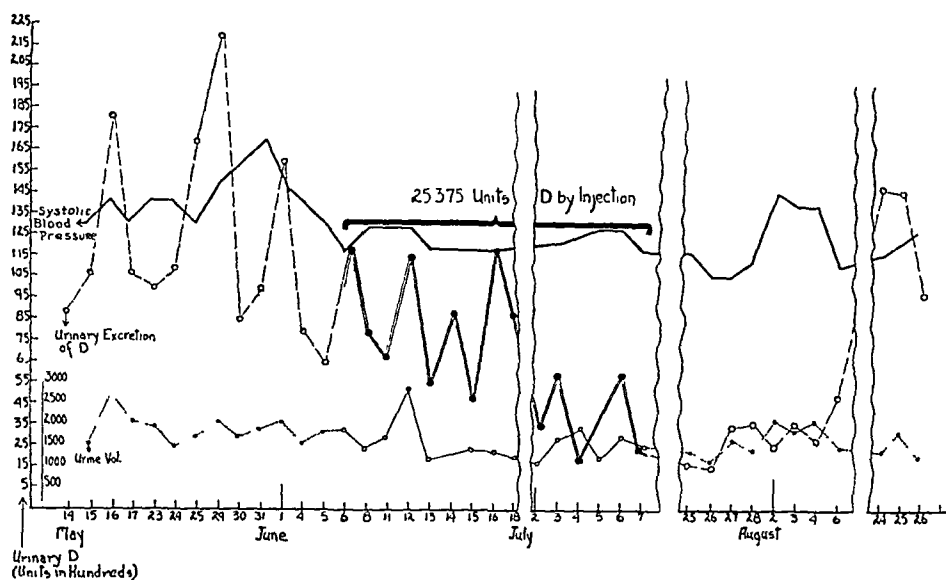


Chart 1—Urinary excretion of the depressor substance by W R. Note that the fluctuations are independent of the volume of urine excreted. In charts 1 to 3 D represents the depressor substance.

another had coronary occlusion. It is unlikely that there was any causal relationship, but these accidents indicated that the natural course of the malady was not stayed by this method of treatment.

Changes in the Urinary Output of the Depressor Substance—The concentration of the depressor substance in the twenty-four hour specimens of urine was determined daily before, during and after treatment in four instances (F S, E W, W R and J K). The changes in the output of urine were of two general types, as shown in charts 1 and 2. In the case of W R (chart 1) the daily concentration of the depressor substance fluctuated widely during the control period, but the average output was less than that of a normal subject of the same age. Shortly after treatment was begun the concentration began to fall, until at the conclusion of the treatment period it had decreased by approximately

80 per cent, at which level it remained for one month. It will be noted that this change was not dependent on a lessened volume of urine. Studies of the renal function, initially showing an excellent renal reserve, were not conducted during the time that the urinary output of the depressor substance was low, so it is impossible to say whether a temporary impairment of renal function existed. It is of interest that the blood pressure was slightly lowered during the period of treatment in this instance. In chart 2 a more irregular type of response is illustrated. The urinary concentration of the depressor substance rose during the early days of treatment from an extremely low initial level. The curve for the excretion then became roughly diphasic. After sinking

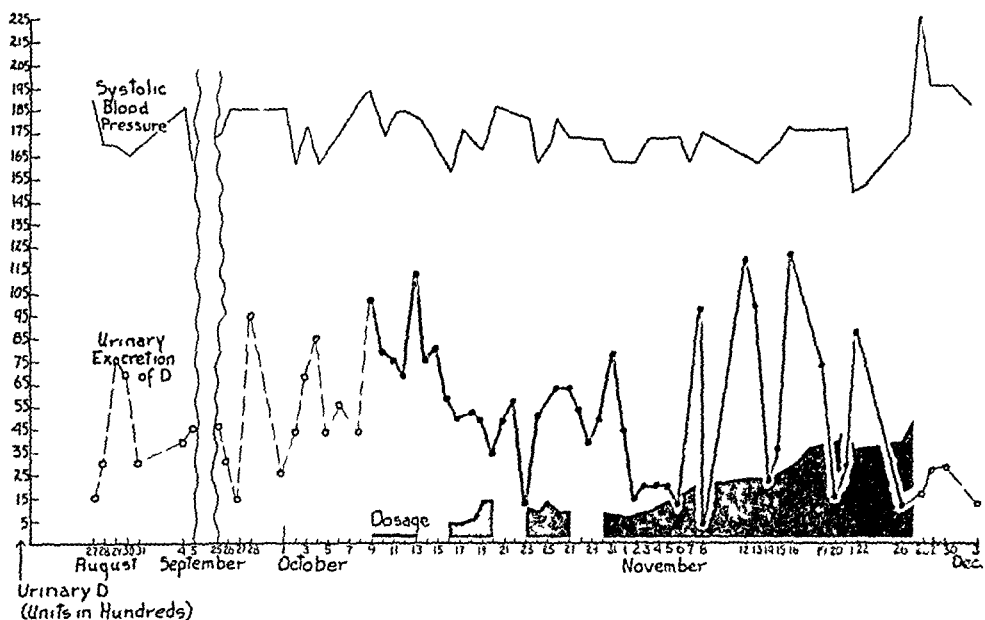


Chart 2—Urinary excretion of the depressor substance by E. W. The period of treatment is represented by double lines and solid circles.

to the control level it rose above this toward the end of the period of treatment, when large doses of the depressor substance were being given. There was no significant change in the blood pressure, except for a final rise when apoplexy supervened. The rate of excretion in the remaining two instances was inconstant, but the shape of the curve was in general similar to that shown in chart 1.

In an attempt to study this matter further, the depressor substance was given to rabbits by the intramuscular and intravenous routes. The total excretion of urine, as measured from samples collected over periods of three days, was followed. A typical protocol is illustrated by chart 3. While the injections were being given there was a pronounced increase in the urinary content of the depressor substance, which in one specimen was twice that of any specimen collected during the control period. The total increase was several times greater than could be accounted for by the total amount of the depressor substance injected. When the

drug was given by the intravenous route, the urinary concentration was extremely depressed during the period of injection and rose to, but not above, the control level when the injections were stopped. We cannot satisfactorily interpret these results, and it is likely that an adequate explanation will not be forthcoming until the level of the depressor substance in the blood can be successfully determined.

It should be added that the samples of urine were tested for depressor activity both before and after boiling. In conformity with our previously reported results, we found that approximately one fourth of the depressor principle was heat stable and that this relationship for the most part held true regardless of fluctuations in the total amount of depressor substance excreted.

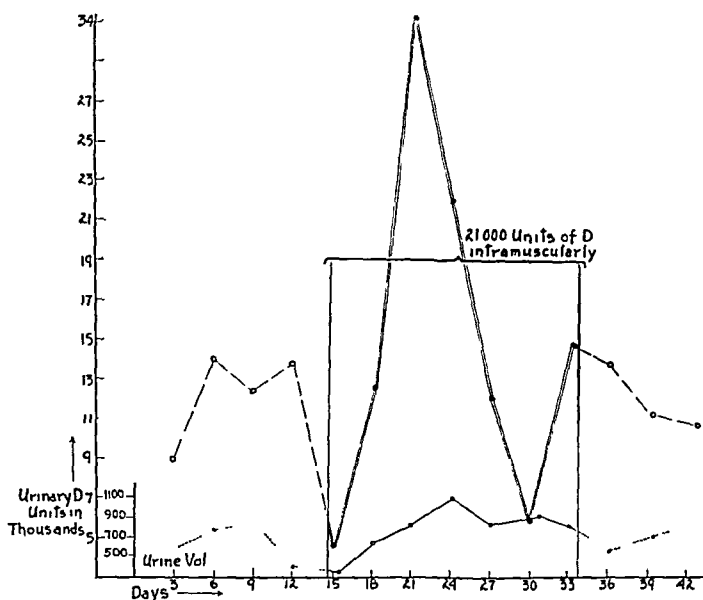


Chart 3—The effect of the intramuscular injection of the depressor substance into a rabbit on the amount excreted in the urine. The period of injection is represented by double lines and solid circles.

COMMENT

The inability of this method of treatment consistently to lower the blood pressure of the patients needs no further comment. The observations on the urinary excretion of the depressor substance have proved disappointing, in that no uniform or predictable trend was discernible. At the outset of this study it was hoped that, coincident with a fall in blood pressure due to the administration of the depressor substance, its urinary output might rise to a normal level and thus confirm a causal relationship between the clinical result and the method of treatment employed. This would have suggested that a restoration to normal equilibrium between pressor and depressor elements of the blood stream

had been accomplished by a true substitution therapy. However, this attractive hypothesis was not confirmed by the results obtained in this study.

SUMMARY

A depressor principle prepared from the urine has been given hypodermically under carefully controlled conditions to ten patients with essential hypertension.

A slight but statistically significant fall in blood pressure resulted in two instances. The blood pressure of the remaining patients was not influenced.

The symptoms presented by these patients were not ameliorated, and there was no indication that the course of the disease was favorably influenced.

In four instances the daily urinary excretion of this substance was determined throughout the period of observation. No consistent change in the concentration could be demonstrated. Similar observations conducted on rabbits likewise were inconclusive.

The use of this principle hypodermically for the treatment of essential hypertension cannot be regarded as a substitutive therapeutic measure.

Progress in Internal Medicine

ALLERGY

A REVIEW OF THE LITERATURE OF 1936

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Another year has gone by since my last review¹ appeared, again a large number of papers on allergy have been published. The *Journal of Allergy* contains many of these. It has an abstract department which has been greatly improved and developed in a wider scope, and it includes also a series of special reviews on certain phases of the study of allergy. Hansel² has written on allergy as related to otolaryngology and ophthalmology, Feinberg³ has reviewed the progress in asthma, Sulzberger⁴ has written on allergy in dermatology, and Walzer⁵ has reviewed the immunology of cutaneous tests. Each of these reviews is good.

In the following summary the selection and arrangement of the material must depend largely on my own personal interest, and I realize that this present combination can satisfy only the general reader. All who are really interested must go to the original sources, which are so easily available. If the attention of the reader, whether general or special, is guided into profitable channels, I shall be repaid for performing a difficult task.

Some progress has been made in the diagnosis and treatment of what may be called clinical allergy, but greater progress has been made in another direction. Allergic conditions, especially hay fever and asthma, are coming to be regarded not so much as separate diseases

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1 Rackemann, Francis M. Allergy. A Review of the Literature of 1935, *Arch. Int. Med.* **57** 184 (Jan.) 1936

2 Hansel, French K. Annual Review of Allergy as Related to Otolaryngology and Ophthalmology. Literature for 1935, *J. Allergy* **7** 164, 1936

3 Feinberg, Samuel M. Progress in Asthma. Literature for 1934 and 1935, *J. Allergy* **7** 268, 1935

4 Sulzberger, Marion B. Allergy in Dermatology. A Discussion of Recent Contributions and Their Relationship to Earlier Dermato-Immunologic Studies, *J. Allergy* **7** 385, 1936

5 Walzer, Matthew. Immunology. A Critical Review of Some Recent Developments in the Field of Allergy, *J. Allergy* **7** 597, 1936

as the outward expression of a peculiar reaction which may after all be merely the exaggeration of a normal response. More and more evidence is at hand of the correlation of the reaction which is termed clinical allergy with similar reactions observed in infectious diseases as well as with other reactions observed in laboratory animals prepared and tested in particular ways. The base on which allergy rests is becoming broader, and the conception of the extent to which allergic reactions occur in the clinic is likewise broader. The relationship of hay fever, asthma, eczema and serum disease to acute infectious processes like pneumonia and trichinosis and to chronic infections like tuberculosis as well as to experimental anaphylaxis is being considered actively. It becomes evident that the study of allergy is not a narrow, specialized field but requires a broad understanding of the behavior of the animal body in its effort to rid itself of foreign proteins under many different conditions.

The immunity of the tissues as opposed to the immunity of the organism as a whole is receiving increased attention. The nature and particularly the function of the local response of the tissues to foreign materials of various kinds applied in various ways are being studied. In the review of last year considerable attention was paid to the observations of Jones and Mote⁶ and others that when a guinea-pig is given repeated daily injections of a foreign protein, like egg white or horse serum, a local reaction is observed as early as the third or fourth day and consists of a red inflammatory lesion, corresponding to the tuberculin reaction. Later, on the seventh or eighth day, the local reaction changes to swelling and edema characteristic of the urticarial reaction which is associated with clinical allergy, and at this same time too, antibodies first appear in the circulating blood. As Dienes⁷ writes in an excellent review of this whole subject, "The first manifestation of the specific response is not the appearance of the antibodies in the circulation but a hypersensitiveness of the tissues." The tissue response comes early and is independent of antibodies. It is not an inflammation in the strict sense but rather an attempt of the body to wall off and localize the infection. It is part of the resistance of the animal. It comes early in the process of immunization and before the development of circulating antibodies. This early tuberculin-like reaction is a function of the tissues themselves and is not in any sense a secondary response dependent on the arrival of antibodies in these tissues. In

6 Jones, T. Duckett, and Mote, John R. The Phases of Foreign Protein Sensitization in Human Beings, *New England J. Med.* **210** 120, 1934.

7 Dienes, L. The Specific Immunity Response and the Healing of Infectious Diseases. Significance of Active Immunity and the Connections Between the Immunity Response and the Anatomic Lesions. *Arch. Path.* **21** 357 (March) 1936.

this way, Dienes explains that the reaction called bacterial allergy represents a true phase in the development of the immune process. It is an indicator of active immunization of the tissues, and it gives rise to those anatomic lesions which serve to localize the infection. Dienes lays some stress on this and justifies his position in several ways, notably by saying that all attempts to produce the tuberculin-like reaction passively with immune serum have failed. This injection of such immune serum results only in the anaphylactic type of response. Desensitization may abolish the urticarial reaction temporarily, but in spite of this a resistance of the tissues persists and can be demonstrated at all times by appropriate treatment. The desensitized animal is not in the condition of a noninfected animal.

Reuben L. Kahn⁸ has recently written a book of seven hundred pages on this subject. In it he too lays stress on the independence of tissue reactions, on the one hand, and systemic reactions as shown by the development of circulating antibodies, on the other. Like the latter, the former also may be highly specific. Kahn emphasizes that allergic reactions, indeed inflammation in general, have a function. The redness and swelling which develop at the site of inoculation represent primarily the effort of the tissue to fix the foreign substance or the bacterium and thus to prevent it from spreading throughout the host. This local immunity varies with certain tissues. The skin, for example, has a much greater reaction capacity (immunity) than does muscle. If staphylococci obtain a foothold in the skin, they are walled off quickly, and the danger to the body as a whole is slight, in the muscle, however, the local response is less violent, and walling off is less efficient. Hence deep staphylococcic infections may be dangerous. The rôle of the tissues in the resistance of the animal is vital. From his studies of tissue reactions Kahn believes that hypersensitiveness, or allergy, is merely an exaggeration of the normal immune process.

The Shwartzman phenomenon is closely related to allergy even though there is still doubt as to its true nature. When an animal (rabbit) is treated with toxin intracutaneously and then after an incubation period receives a dose of that same toxin intravenously, the treated cutaneous sites will show an extensive reaction, with severe inflammation and necrosis. As is well known, this reaction is produced by specific and also by nonspecific means. Jules Freund,⁹ for example, has shown in rabbits that the intravenous injection of starch will cause a reaction to appear at the site of a previous intracutaneous dose of

8 Kahn, Reuben L. *Tissue Immunity*, Springfield, Ill., Charles C. Thomas, Publisher, 1936.

9 Freund, J., and Hosmer, E. P. Hemorrhagic Reaction [Shwartzman Phenomenon] at the Site of Injection of Toxins After Intravenous Injection of Starch in Young and Adult Rabbits, *J. Immunol.* **29**: 279, 1935.

toxin. In another experiment he has shown that when filtrates of various organisms are injected intravenously the treatment will result in violent lesions at the site of previous cutaneous tests with tuberculin, horse serum or silver nitrate. Incidentally, these toxins cause much more reaction in tuberculous than in normal animals. By means of the Schwartzman reaction, various attempts have been made to explain the mechanism and clinical pictures of common diseases. Last year for example, the interpretation of a syphilitic chancre on this basis was described. Now comes a report from Sanarelli¹⁰ in a letter published in *The Journal of the American Medical Association*, that various acute disturbances characterized by hemorrhage and necrosis, such as cholera or even appendicitis, may depend on a local sensitiveness of the tissue, which is lighted up by the sudden presence of toxic substances in the blood stream.

In all studies of allergy in animals as well as in man, the experimental technic is of greatest importance. McEwen and Swift¹¹ describe their studies of the reactions of rabbits to the injection of bacterial substances. When their animals were treated intravenously, serum antibodies reached a high titer, but the extent of the cutaneous hypersensitiveness was only moderate. The cutaneous reactions were immediate and of an urticarial type. When, however, other animals were treated intracutaneously, hardly any circulating antibodies developed, while the cutaneous tests showed a strongly positive reaction of the delayed tuberculin-like type. When whole organisms, that is, formed elements, were used for the preparation, more circulating antibodies (precipitins) developed, and the cutaneous tests of the immediate type showed positive reactions to the protein P and the carbohydrate S fraction as well as to the whole organism. When however, the original treatment was with the P fraction or the S fraction alone, then the reactions in both serum and tissues were chiefly to the particular fraction used. The work indicates that the induction of reactions of the immediate type requires something more than the presence of a high serum precipitin titer to the substance in question. Cutaneous reactions and serum antibodies are not always parallel.

Stevens and Jordan¹² describe the results of tests with various bacterial nucleoproteins in patients with asthma. They too show that

10 Hemorrhagic Allergy, foreign letter, J A M A **107** 1825 (Nov. 28) 1936

11 McEwen C, and Swift H F. Cutaneous Reactivity of Immune and Hypersensitive Rabbits to Intradermal Injections of Homologous Indifferent Streptococcus and Its Fractions, J Exper Med **62** 573, 1935

12 Stevens, F A, and Jordan, L. Behavior of Immediate and Delayed Cutaneous Reactions to Bacterial Nucleoproteins in Asthmatic Patients, J Immunol **31** 51, 1936

delayed inflammatory reactions and immediate urticarial reactions are closely related, as will be described presently

In making an analysis of experiments of this kind, the student must note several important points the choice of animal, the treatment by which sensitiveness is produced and, finally, the material used and the method of application to elicit the reaction Apparently it is true that the urticarial reaction occurs only when the preliminary treatment has resulted in the production of circulating antibodies In animals inoculated with living organisms or with whole killed organisms (formed elements) immunity of this sort is produced and cutaneous tests of the immediate type can be readily demonstrated When, however, the animals are treated with extracted material, such as bacterial nucleoprotein, a delayed cutaneous reaction, of slight extent, is often observed, the urticarial reaction, never Under special conditions, treatment with a carbohydrate substance alone may result in the production of an immediate reaction Are these new reactions temporary or permanent? How long can they be demonstrated in the animal or in the patient? Mote and Jones¹³ followed their original patients for two years and found that with the passage of time the urticarial reaction observed at the height of the response fades off slowly until all that is left is a small, red, inflammatory, tuberculin-like response to the test dose Simultaneously, the antibodies disappear slowly from the serum in corresponding fashion This, in itself, is some evidence that the relation between the delayed inflammatory reaction and the immediate urticarial reaction depends on a quantitative rather than a qualitative basis

Stevens and Jordan¹⁴ have studied the reactions of asthmatic patients to various bacterial substances injected intracutaneously In their patients the findings were much the same as in the experimental animals, except perhaps that in the patients the individual variations were greater Immediate and delayed reactions occurred at the same time and to the same organism More commonly, however, the nucleoprotein of one culture showed a delayed reaction while a similar preparation from another showed an immediate response The authors studied also the duration of their tests and made the interesting observation that when once the tendency to give an immediate or delayed reaction was acquired, a similar response was obtained when the reaction was elicited at a later period This fact fits in with the clinical

13 Mote, John R, and Jones, T Duckett The Development of Foreign Protein Sensitization in Human Beings, *J Immunol* **30** 149, 1936

14 Stevens, F A, and Jordan, L Reactions to Intracutaneous Injections of Nucleoproteins of the Upper Respiratory Pathogenic Bacteria in Asthmatic Patients *J Allergy* **7** 443, 1936

observation that in many chronic diseases the reactions to new and recurrent attacks are much like the old reactions. Thus, in rheumatic fever a new cold will cause a new flare-up in the joints, whereas in asthma a new cold will cause bronchospasm. Incidentally, Krause¹⁵ observed some time ago that a new attack of bronchitis is likely to begin in precisely the same part of the lung as the former attack. In allergy, one speaks of shock tissues in the effort to explain why it is that of two subjects sensitive to pollen, one will have hay fever and the other asthma. Obviously, the differences depend on changes in the tissue reactivity of certain areas.

Swift and Schultz¹⁶ have worked on the synergic effect of two substances affecting the animal at the same time. They have confirmed the findings of Burky that the capacity of beef lens extract to produce sensitiveness in rabbits is greatly enhanced if the extract is mixed first with staphylococcus toxin. Furthermore, the effect is observed even if the two substances are injected separately and perhaps with an interval of several hours between the doses. If the animal is immune to staphylo toxin, the toxin is neutralized in vivo, and the synergic effect is lost. Neutralization in the test tube, however, does not prevent the reaction. In other experiments Swift and Schultz¹⁷ found that the addition of horse serum likewise increased the antigenicity of the lens extract, although to a less extent than did the addition of toxin. In discussing their observations, the authors state their belief that the toxin probably acts as a stimulant to the antibody-producing cell rather than makes a new combination with the antigen. That neutralized toxin will work as well as native toxin and that horse serum also is effective is interesting even though the reason is obscure.

The pneumococcus remains the favorite object of study, no doubt because its specific capsular substance is well defined and can be separated from the bacterial protein. The chemical methods of this procedure have been revised and improved by Heidelberger and his co-workers¹⁸

15 Krause, A. K. Chronic Pulmonary Infections in Childhood. *Ann. Int. Med.* **4** 1424, 1931.

16 Swift, H. F., and Schultz, M. P. Studies in Synergy. The Synergic Action of Staphylo toxin and Beef Lens Extract in Rabbits, *J. Exper. Med.* **63** 703, 1936.

17 Swift, H. F., and Schultz, M. P. Studies in Synergy. Synergic Stimulating Effect of Hypersensitivity to Foreign Protein and to Bacteria. *J. Exper. Med.* **63** 725, 1936.

18 Heidelberger, M., Kendall, F. E., and Scherp, H. W. The Specific Polysaccharides of Types I, II and III Pneumococcus. A Review of Methods and Data, *J. Exper. Med.* **64** 559, 1936.

Harley¹⁹ has studied the relationship of allergy, anaphylaxis and immunity to pneumococci and has found another factor in the technic Treatment with virulent S forms containing the soluble specific substance will prepare the animal so that it will react later to cutaneous tests with the carbohydrate On the other hand, treatment with avirulent R forms does not have such an effect, although in this case a sensitiveness to the somatic P fraction can be demonstrated Treatment with the whole vaccine results in responses which are variable, because obviously the material used is a mixture Harley's article contains a number of interesting charts

The mechanism of desensitization in anaphylaxis has been studied by Morris²⁰ Long ago, Richard Weil²¹ pointed out that passively sensitized guinea-pigs can be protected against shock by an excess of antibody, and Dale and Kellaway²² demonstrated that a reaction of the sensitized uterus can be prevented by adding antibody to the bath Morris repeated these old experiments but could not confirm them After the treatment of sensitized animals with immune serum, the reactivity was reduced a little but not much Furthermore, Morris showed that some protection could be obtained by nonspecific means, with salts and lipids and with foreign serum which was nonspecific This protection was temporary, and soon sensitiveness reappeared, no doubt because of the persistence of traces of antigen in the original sensitizing serum She argues that if desensitization was due to the saturation of cellular antibodies by a sublethal dose of antigen, then additional antibodies should resensitize the animal The fact is, however, that attempts to resensitize were ineffective Guinea-pigs passively sensitized with antipneumococcus horse serum were desensitized with the bacterial carbohydrate substance and then were given a supposedly shocking dose of normal horse serum Nothing happened The cellular antibody was not blocked In the reverse experiments, Morris could show that animals passively sensitized with the same antipneumococcus serum and then desensitized with horse serum could withstand multiples of the fatal dose of the pneumococcus carbohydrate Their reactivity had been reduced so that allergy was no longer important, but their resistance to infection was still at a high level In spite of the fact that

19 Harley, D Pneumococcal Allergy, Anaphylaxis and Immunity, *J Path & Bact* **41** 491, 1935

20 Morris, Marion C The Relation Between Antianaphylaxis and Antibody Balance I The Role of Excess of Circulating Antibody in Hypersensitiveness, *J Exper Med* **64** 641, 1936, II The Effect of Specific Desensitization upon Resistance to Infection and upon Antibody Balance, *ibid* **64** 657, 1936

21 Weil, Richard Anaphylaxis, *J M Research* **30** 299, 1914

22 Dale, H H, and Kellaway, C H Anaphylaxis and Immunity in Vitro, *J Physiol* **54** cxliii, 1921

the animals had been desensitized, a different test showed that the antibody content was not depleted. In these experiments dealing with carbohydrate and the immediate reaction to it, it appears that desensitization is not concerned with a reduction in antibody but depends on some other change, a nonspecific one, in the animal. In studying the disappearance of a reaction to the tuberculin test during fever, Pilcher²³ found that the reaction to the cutaneous test with codeine, which is positive in most normal persons, became negative during the fever and the rash of measles and scarlatina. The liberation of H substance had induced a refractoriness to whealing.

Mills and Dragstedt²⁴ made an attempt to produce a blockade of the reticulo-endothelial system with india ink, but in spite of this treatment it was easy to sensitize the animals to horse serum and later to cause anaphylaxis in them. Incidentally, Gernez²⁵ had the interesting idea of mixing serum with fatty substances in order to delay absorption. Mixtures of horse serum with hydrous wool fat or olive oil resulted in sensitization as usual and in comparable doses, but when sensitized animals were treated with the mixture subcutaneously and then several hours later were given a fatal dose of horse serum intravenously, half of them survived. Specific desensitization had been accomplished to some extent, showing that the oil had delayed the absorption. In considering experiments on anaphylaxis in guinea-pigs, the findings of Zinsser and Enders²⁶ are interesting. The authors could show that in the passive anaphylaxis experiment the time factor is not necessary. If the antibody and the antigen are both given intravenously, reactions will occur even though the two materials are injected at the same time, indeed the antibody may be injected some time after rather than before the antigen. However this "reversed" passive anaphylaxis can be demonstrated only in certain breeds of guinea-pigs.

A little more light has been thrown on the background of allergy. It is conceivable that a vitamin deficiency could explain the incidence of clinical hypersensitiveness. Hochwald²⁷ studied the antiallergic

23 Pilcher, J. D. Local Skin Reactions in Measles and Scarlet Fever in Relation to the Intracutaneous Tuberculin Reaction, *Am Rev Tuberc* **31** 568 1935

24 Mills, Moore A., and Dragstedt, Carl A. The Reticulo-Endothelial System and Anaphylaxis in the Dog, *J Immunol* **31** 1, 1936

25 Gernez, C. Attempts at Anaphylactic Sensitization and Desensitization of Guinea-Pigs by Mixtures of Serum and Lanolin (Hydrous Wool Fat), *Compt rend Soc de biol* **120** 186, 1935

26 Zinsser, H., and Enders, J. F. Variations in the Susceptibility of Guinea Pigs to Reversed Passive Anaphylaxis, *J Immunol* **30** 327, 1936

27 Hochwald, A. Antiallergic Properties of Vitamin C *Zentralbl f inn Med* **56** 769, 1935

properties of vitamin C and found that when 100 mg of cevitamic acid was given to sensitized guinea-pigs a few minutes before the shocking dose, 18 of 29 animals had no symptoms. However, if the vitamin was given from two to four hours beforehand, no protection resulted. In other experiments, Hochwald found that treatment with glutathione shortly before the shocking dose also gave protection. Since the short interval of time is so important, the author concludes that protection of this sort cannot depend on vitamin storage but must be based on a mechanism similar to that of protection which follows the injection of various colloidal substances.

Solomonica,²⁸ working with vitamin C, obtained different results. In his work the time relation was different. When his animals were given doses of vitamin C subcutaneously prior to and during the sensitizing period, many of them survived. If, however, the doses were given during the last two weeks or only shortly before shock, the protection was much less. Solomonica's experiments were suggested by the observation that such endocrine preparations as anterior pituitary extracts and estrogenic substances seemed to inhibit anaphylactic shock, and he thought that the reasons might depend on the known fact that each of these preparations contains quantities of vitamin C.

Comparative studies of the rat and guinea-pig have long been contemplated because of the striking contrast in the immunologic behavior of the two animals. Pratt²⁹ was successful in producing symptoms of anaphylaxis in white rats, but none of his animals died, and all efforts to demonstrate specific reactions in the isolated uterus were unsuccessful.

Granted an allergic animal, how does sensitization develop? Ten years ago Matthew Walzer³⁰ describe an observation which is of real importance in suggesting a method of approach to a better knowledge of the physiology of the absorption of protein. He presented evidence that under certain circumstances protein can be absorbed unchanged into the blood stream. Since Walzer's first demonstration, it has been found that if small doses of serum from highly sensitive patients are injected into the skin of normal human recipients, according to the method of the Prausnitz-Kustner experiment, specific reactions can be produced in the spot of injection by treatments of three kinds. 1. Walzer fed the antigen (egg white or fish) to a fasting subject. 2. L. N.

28 Solomonica, B. Vitamin C and Anaphylactic Shock in Guinea Pigs, *J Immunol* **31** 209, 1936.

29 Pratt, Henry N. Studies of Anaphylaxis in the Albino Rat with Reference to Diet and Histamine, *J Immunol* **29** 301, 1935.

30 Walzer, M. A Direct Method of Demonstrating Absorption of Incompletely Digested Proteins in Normal Human Beings, *J Immunol* **11** 249, 1926.

Grav³¹ injected the antigen (ragweed) subcutaneously 3 M B Cohen³² used inhalation of the antigen (ragweed) in the form of crude dry pollen. In each case there was a flare-up in the passively sensitized skin. These experiments were described in the review of the literature of 1935. They are interesting partly because they point to a common principle in the production of allergic symptoms following contact with the allergen and partly because they suggest that the antigen itself—even in spite of being in such an enormous molecule as egg globulin—is absorbed unchanged into the blood stream. Walzer³³ has recently published his seventh paper on this problem, in it he shows that when the stomach is hyperacid the appearance of the cutaneous reaction is delayed for from an average of seventeen minutes to twenty-four minutes. Alexander, Shirley and Allen³⁴ have investigated the route by which native protein can enter the blood. To dogs that had fasted for twenty-four hours they fed egg white in moderate doses, and three hours later they killed the animals with ether. Using rabbit antiegg serum of high potency, they could demonstrate a positive reaction to the precipitin test for the antigen (egg) in the lymph and in the systemic blood but not in the portal blood. Furthermore, both the lymph and the systemic blood caused reactions in isolated skin of sensitized guinea-pigs and also in human skin passively sensitized with the serum of patients sensitive to egg. Alexander concludes that the absorption of the ingested protein is by way of the thoracic duct. Somewhat in line is the observation by Marks³⁵ that a positive reaction to the test for egg white in the urine, also by means of highly potent antiegg serum is obtained in less than 20 per cent of patients with a normal alimentary tract but in 75 per cent of patients afflicted with active peptic ulcer. The results are so striking that the author advises the test as an additional method of diagnosis in gastric disease.¹ The conclusion is hard to correlate with that of Walzer.

31 Grav, L. N. The Passive Transfer of Hypersensitiveness (Local and Contralateral Passive Transfer Experiments), *Bull Johns Hopkins Hosp* **40** 270, 1927

32 Cohen, M. B., Ecker, E. E., Brethart, I. R., and Rudolph, J. A. The Rate of Absorption of Ragweed Pollen Material from the Nose, *J Immunol* **18** 419, 1930

33 Walzer, M., and Grav, I. Studies in Absorption of Undigested Protein in Human Beings. VII Absorption of Unaltered Protein Introduced by Duodenal Tube into the Abnormal Gastro-Intestinal Tract, *J Allergy* **8** 81, 1936

34 Alexander, H. L., Shirley, K., and Allen, D. The Route of Ingested Egg White to the Systemic Circulation, *J Clin Investigation* **15** 163, 1936

35 Marks, M. B. Permeability to Egg Albumin in Peptic Ulcer. Possible Test for Activity of Peptic Ulcers, Preliminary Report, *Am J Digest Dis & Nutrition* **3** 41, 1936

CHEMISTRY OF SENSITIZATION

The chemistry of sensitization with nonbacterial substances has been developed further. Landsteiner and Jacobs³⁶ have published three papers on the sensitization of animals with simple chemical compounds. In a series of experiments they have shown that artificial sensitiveness can be produced in rabbits by a variety of substances having a relatively simple chemical structure, the requirement being that these substances must be combined with protein. After sensitization the reaction can be demonstrated by applying the substance alone either by injection or by painting it on the unbroken skin. Such experiments are successful according as the chemical structure of the substance permits of its combination with proteins. Experiments with urushiol which is contained in lacquer showed a close relation between the sensitizing power and the ability of the substance to make substitution compounds with aniline. Dinitro and trinitro compounds have this ability, but dichloronitro compounds which are already saturated do not react. In the third paper the authors report on anaphylaxis induced by arsphenamine. When the drug was used in its original and unneutralized form to sensitize guinea-pigs by two intradermal doses, a later treatment given intravenously resulted in anaphylactic shock in over half the animals. Thus there is evidence that the development of sensitiveness depends on the ability of the particular substance to form combinations with protein, that is to say its own stability.

Meantime Caulfeild³⁷ has made a great advance by showing that when potassium alum is added to pollen extract a suspension of the flocculent precipitate can induce anaphylactic sensitiveness when injected into guinea-pigs. Whether this alum has a chemical effect or whether the results depend merely on a physical change is a question for future study.

Somewhat similar is the finding of Spain and Newell³⁸ that when house dust is filtered through cellophane under great pressure the filtrate is inert whereas the residue remains active. In this instance also the increase of activity depends on a physical change. Incidentally the activity of the fractions seemed to be proportional to the amount of nitrogenous material precipitable by trichloro-acetic acid. There was no correspondence between the degree of activity and the amount of

³⁶ Landsteiner K, and Jacobs, J. Studies on the Sensitization of Animals with Simple Chemical Compounds, *J Exper Med* **61** 643 1936, II *ibid* **64** 625 1936, III Anaphylaxis Induced by Arsphenamine *ibid* **64** 717 1936

³⁷ Caulfeild, A H W. Brown M H and Waters, E T. Alum as an Adjuvant in Sensitizing Guinea Pigs to Ragweed Pollen (*Ambrosia Artemisiifolia*), *J Allergy* **7** 451, 1936

³⁸ Spain, W C, and Newell I M. Ultrafiltration of House Dust Extracts *J Allergy* **7** 134 1936

nitrogen precipitable by phosphotungstic acid Osgood and Hubbard³⁹ have come to a similar conclusion in their claim that precipitation with trichloro-acetic acid provides a better measure of skin test activity in extracts of ragweed pollen

CLINICAL ALLERGY

Diagnosis—The diagnosis of the exciting cause of symptoms by means of cutaneous tests is still a dramatic procedure However, as knowledge increases these tests lose some of their glamour Alexander⁴⁰ recites the difficulties He explains that localized allergy is the rule rather than the exception and asks

Need we always expect that when the shock organ is the lung or the nose or perhaps the blood vessels in the deeper layers of the skin (urticaria) the skin will also and that it be sensitive sufficiently to reveal a positive skin test? Is it surprising that patients are clinically sensitive even though their skin tests are negative?

The fact remains that this discrepancy is always hard to prove by experiment even though clinically the demonstration seems easy, as when the elimination of some food or dust relieves the symptoms Meantime, the contrary difficulty is much more common and is easy to demonstrate Positive reactions to cutaneous tests with no accompanying clinical symptoms are a common finding

In a study of 32 employees in a bakery Colmes and his associates⁴¹ found that 6 men showed a positive cutaneous reaction to wheat, but that only 2 of them had symptoms of sensitivity The difference between the development of a positive reaction to a cutaneous test and the development of symptoms is real, but whether it represents more than a quantitative variation is uncertain

In normal persons positive reactions to cutaneous tests made with routine allergens are common In his review of the mechanism of cutaneous tests, Walzer² says that he is disturbed by the large number of positive results obtained in normal persons as reported in the literature and suggests that either the technic is faulty or the subjects are truly allergic but with a low degree of reactivity Formerly Simon and I⁴²

39 Osgood, Howard, and Hubbard, Roger S Skin Exciting Activity of a Ragweed Pollen Extract as Measured by Its Content of Three Nitrogen Fractions, *J Allergy* 7 112, 1936

40 Alexander, H L Interpretation of the Skin Test Used in Allergic Disorders, *Journal-Lancet* 56 131, 1936

41 Colmes, A, Guild, B T, and Rackemann, F M Studies in Sensitization, *J Allergy* 6 539, 1935

42 Rackemann, F M, and Simon, F A Technic on Intracutaneous Tests and Results of Routine Tests in Normal Persons, *J Allergy* 6 111, 1935

noted positive reactions in 50 per cent of normal persons. Now, Grow and Herman⁴³ report positive reactions in 55 per cent of 150 normal persons. Most of the reactions in our series were to kapok cotton, feathers and house dust, and as H. N. Pratt suggested in the course of a conversation, why should it not be that many, if not all, persons have a tendency to become slightly sensitive to those substances to which they are exposed in some quantity every day? The extracts are not irritating, there are plenty of normal controls and the differences between the reactors and the controls are definite. Pratt's suggestion is interesting and finds support in the observations of Salén and Juhlin-Dannfelt⁴⁴. These authors tested 432 persons belonging to different occupational groups and found that the presence of positive reactions to cutaneous tests corresponded closely with the respective occupations. Bakers reacted to wheat but not to horse dander, grooms reacted to horse dander and not to wheat. The idea fits in with the well known principle that children become sensitive to foods while adults become sensitive to dusts. O'Keefe⁴⁵ presents new figures on this point. Similarly, Parlato⁴⁶ points to the great frequency of positive reactions to tests with extracts of raw silk—of 166 allergic subjects, 33 per cent reacted to silk, whereas of 102 nonallergic subjects, 27 per cent reacted. Note that at least two thirds of the subjects showed no reaction. Pratt⁴⁷ finds that 79 per cent of children who have perennial asthma react to house dust.

The leukopenic index which Vaughan has studied with such enthusiasm has been doubted, and an editorial⁴⁸ in *The Journal of the American Medical Association* points out that under normal conditions the total leukocyte counts may show even wider fluctuations than do the counts in Vaughan's curves. The editorial includes a good bibliography. In the meantime, Rinkel⁴⁹ has found that Vaughan's method is of practical value. He found that postcibal leukocytosis was associated with foods not producing symptoms, whereas leukopenia was

43 Grow, Max H., and Herman, Nathan B. Intracutaneous Tests in Normal Individuals, *J. Allergy* **7** 108, 1936

44 Salén, E. B., and Juhlin-Dannfelt. The Occurrence of So-Called Latent Allergy, *Acta med. Scandinav.* **86** 505, 1935

45 O'Keefe, Edward S. An Analysis of Three Hundred Cases of Asthma in Children, *New England J. Med.* **214** 62, 1936

46 Parlato, Salvatore J., and Swarthout, G. A Study of the Silk Allergen, *J. Allergy* **5** 505, 1934

47 Pratt, Henry N. House Dust Hypersensitivity in Perennial Asthma of Childhood, *J. Allergy* **8** 60, 1936

48 The Leukopenic Index and Food Allergy, editorial, *J. A. M. A.* **106** 1988 (June 6) 1936

49 Rinkel, H. I. Leukopenic Index in Allergic Diseases, *J. Allergy* **7** 356, 1936

associated with symptoms. With this method, in several cases intractable asthma was cleared up promptly when the leukopenic index was used as an adjunct to other tests.

When all is said and done, the fact remains that the clinical history is the one important method in the diagnosis of the cause of symptoms in patients with clinical allergy. Recently, I⁵⁰ have described the "tricks" in history taking.

The results of cutaneous tests in infectious diseases with specific bacterial products deserve study because these diseases represent a relatively pure type of sensitization. In trichinosis, for example, the original observations of Bachman,⁵¹ that the edematous reaction often with hemorrhage is easily developed in rabbits infected with *Trichinella*, has been studied in detail by Augustine and Theiler,⁵² as described in previous reviews. Now comes a paper by Goldschlager⁵³ which confirms these reports and stresses the diagnostic importance of the immediate cutaneous reaction to an extract of trichinellas and which, as expected, develops at the same time that precipitins first appear in the circulating blood.

The Frei test for lymphogranuloma venereum is similar in general, but this test is based on a reaction of the delayed inflammatory type. Gray and his associates⁵⁴ applied it to 790 patients in St. Louis and found positive results in 3.4 per cent of the white population and in 40 per cent of the colored population. However, many of the subjects who showed a positive reaction revealed no clinical manifestation of the disease. Similar is the report by Cole and Levin⁵⁵ on the intradermal reaction for chancroid. Like the Frei test, this new chancroid test is specific; the reaction is delayed and inflammatory. This test and the Frei test, too, may show positive results for many years after the disease has passed.

The relation between allergy and diabetes is said to be antagonistic, as though insulin and epinephrine counteracted each other. Among

50 Rackemann, Francis M. History Taking in Allergic Diseases, *J. A. M. A.* **106** 976 (March 21) 1936.

51 Bachman, G. W. Intradermal Reactions in Experimental Trichiniasis. Preliminary Report, *J. Prev. Med.* **2** 169 and 513, 1928.

52 Augustine, D. L., and Theiler, Hans. Precipitins and Skin Tests as Aids in Diagnosing Trichinosis, *Parasitology* **24** 60, 1932.

53 Goldschlager, A. I. Trichinosis. A Report of Eight Cases with Skin and Precipitin Tests, *Ann. Int. Med.* **8** 939, 1935.

54 Gray, S. H., Hunt, G. A., Wheeler, P., and Blache, J. O. Lymphogranuloma Inguinale. Its Incidence in St. Louis, *J. A. M. A.* **106** 919 (March 14) 1936.

55 Cole, H. N., and Levin, E. A. The Intradermal Reaction for Chancroids with Chancroidal Bubo Pus, *J. A. M. A.* **105** 2040 (Dec. 21) 1935.

1,240 diabetic patients König⁵⁶ found only 3 instances of this type Wilmer⁵⁷ has claimed that allergic subjects can utilize more sugar than normal subjects (their curve for sugar is lower) MacQuiddy, McIntyre and Koser⁵⁸ found no difference in the level of the blood sugar during fasting between normal subjects and allergic subjects Meantime, however, the injection of dextrose intravenously has been shown by many authors to be an important therapeutic adjunct in patients with intractable asthma Conversely, Wegierko⁵⁹ has treated 40 patients by means of insulin shock, giving them 40 units of insulin before breakfast, preferably during an attack of dyspnea from the asthma He observed that insulin shock stopped the attack of dyspnea

HAY FEVER

The mechanism of treatment remains obscure Last year Cooke, Barnard, Heald and Stull⁶⁰ showed that when the blood serum of a patient with hay fever was obtained before treatment and then mixed and incubated with pollen extract (ragweed) and the mixture was then injected into the skin of a normal subject, a positive reaction resulted, and forty-eight hours later a test of this site showed a negative Prausnitz-Kustner transfer reaction The transferring antibody in the serum had been neutralized by the ragweed so that it was no longer active When, however, the same patient was treated successfully with pollen extract, a mixture of his serum with ragweed resulted in negative reactions after the preliminary injection into the normal subject, and the later test with ragweed then gave positive results These findings were interpreted as evidence that in the course of treatment a new antibody was developed which had the power to prevent the union of antigen and antibody In the serum after treatment the antibody was left free to sensitize the sites in the normal subject If these observations can be repeated by other workers, they are, of course, of great importance

56 König, F Concurrence of Diabetes Mellitus and Bronchial Asthma, *Med Klin* **31** 545, 1935

57 Wilmer, H B , Miller, M M , and Beardwood, J T Recent Advances in the Diagnosis and Treatment of Allergic Disease, with Special Reference to Glucose Tolerance and Metabolism, *South M J* **29** 197, 1936

58 MacQuiddy, E L , McIntyre, A R and Koser, Don Blood Sugar Studies in Hay Fever and Asthma, *J Allergy* **7** 471, 1936

59 Wegierko, J Favorable Influence of Hypoglycemic State Following Administration of Insulin on Evolution of Bronchial Asthma *Cases, Presse med* **43** 1379, 1935, Treatment of Bronchial Asthma by Insulin Shocks, *ibid* **44** 731, 1936

60 Cooke, R A , Barnard, J H , Heald, S , and Stull, A Serological Evidence of Immunity with Coexisting Sensitization in a Type of Human Allergy (Hay Fever), *J Exper Med* **62** 733, 1935

Meantime Wagner and I⁶¹ have made a study of the crossed reactions between the pollens of different grasses. Cutaneous sites in normal recipients were passively sensitized with the serum of those patients who were sensitive to a number of grass pollens at the same time, and on the following day these several sites were desensitized by repeated doses of one grass and then tested with another grass. In many instances this later test gave a negative result—a crossed relationship could be demonstrated, but the relationships were not constant and it was concluded that pollens contain both a specific factor and a group factor.

In another study⁶² it was desired to throw light on the mechanism of desensitization by repeated treatment of single sites in patients who had hay fever and were actively sensitive. Repeated treatment of this sort did result in desensitization, but when the strength of the extract used was increased new reactions occurred. Furthermore, if a day or two was allowed to intervene before the next treatment, the subsequent injection was likely to give a positive reaction. To us it was clear that desensitization of this kind was merely a quantitative change and was only temporary.

The perennial treatment of pollen allergy has many adherents. Peshkin⁶³ however believes that preseasonal treatment is still satisfactory. However there are patients who do badly when the pollen extract is given shortly before the season and then are much better when in another year the pollen extract is given in regular monthly doses. More direct is the evidence presented by Vander Veer,⁶⁴ in which he shows that in a large series of cases the results with perennial treatment were better on the whole, although the percentage figures show that the amount of improvement was not great. Levin⁶⁵ studied the effect of massive doses of pollen extract on the size of the cutaneous reaction and found that it became negative in 14.9 per cent of cases. Sometimes clinical relief occurred without much change in the cutaneous

61 Rackemann, F. M. and Wagner, H. C. The Desensitization of Skin Sites Passively Sensitized with Serum of Patients with Hay Fever. Crossed Reactions of Different Pollens, the Variations in the Recipient, *J. Allergy* **7** 319, 1936.

62 Wagner, Harold C., and Rackemann, F. M. Studies in Hay Fever. Specific Desensitization of Skin Sites in Actively Sensitized Persons, *J. Allergy* **7** 543, 1936.

63 Peshkin, M. M. Critique of the Perennial Treatment of Pollen Allergy, *J. Allergy* **7** 477, 1936.

64 Vander Veer, Albert. The Relative Merits of Seasonal and Perennial Treatment of Hay Fever, *J. Allergy* **7** 578, 1936.

65 Levin, Samuel J. The Effect of Massive Pollen Therapy on Skin Test Sensitivity, *J. Allergy* **8** 26, 1936.

reactivity Results with pollen treatment are given by Ellis,⁶⁶ who stresses the use of mixtures of extracts made up according to the degrees of sensitiveness to different pollens Of 143 patients, 40 per cent were completely relieved, and another 30.8 per cent secured marked relief

Ionization treatment of hay fever has given disappointing results Ramirez⁶⁷ observed 75 patients who received this treatment, in every case the treatment was a failure Bernheimer⁶⁸ points to the risk of complications from a procedure of this sort Vistreich⁶⁹ suggests the application of phenol to the nasal mucosa, claiming over 90 per cent relief in 75 per cent of 28 cases For a time after the treatment, the mucosa was less sensitive to the application of dilutions of pollen, but the time was short

Hodgson⁷⁰ gives a botanic survey of the island of Bermuda Dwarf ragweed is scarce The grass group occurs in insignificant amounts It is Bermuda cedar pollenating in March which causes most of the trouble on the island

ASTHMA

The mechanism of an attack of asthma is not yet understood Walzer⁷¹ reviews the arguments for the theory that the attack depends on spasm of the bronchial muscles and for the other theory that edema of the mucous membrane is responsible The present evidence favors the latter theory strongly Edema is the characteristic lesion in other manifestations of allergy as well as in the local allergy produced passively Other findings support the edema theory At autopsy the plugs of sticky material in all the smaller bronchi are the characteristic findings, as Wilmer and his associates⁷² describe once more and as I have seen repeatedly in fatal cases Hypertrophy of the bronchial glands is a common finding, and Dr Mallory will describe it soon This

66 Ellis, R. V. Results Obtained in Treatment of Hay Fever with Pollen Extracts, *Minnesota Med* **19** 507, 1936

67 Ramirez, M. A. Disappointing Results from the Ionization Treatment of Hay Fever, *J. A. M. A.* **106** 281 (Jan. 25) 1936

68 Bernheimer, Leopold B. Zinc Ionization in Nasal Allergy, *J. A. M. A.* **106** 1980 (June 6) 1936

69 Vistreich, F. The Effect of Intranasal Phenol Application in Hay Fever Quantitatively Studied by a New Intranasal Swab Test with Pollen Extracts, *Laryngoscope* **46** 717, 1936

70 Hodgson, H. Report of Botanical Survey of Bermuda, New York State *J. Med.* **35** 27, 1935

71 Walzer, M. The Mechanism of the Paroxysm in Bronchial Asthma, *Journal-Lancet* **56** 117, 1936

72 Wilmer, H. G., Eiman, J., and Miller, M. M. Pathologic Picture in a Case of Essential Bronchial Asthma. Roentgen Findings Ante and Post Mortem, *J. Allergy* **7** 156, 1936

glandular hypertrophy with the resulting dense exudate, containing mucus, fibrin and eosinophilic debris, is much more striking than is the evidence of hypertrophy of the muscles. During life the physical signs change rapidly from one portion of the lung to another, obviously because these same mucus plugs form and then loosen, now in this area now in that. When the obstruction from the plug is partial, emphysema develops behind it, but when the plugging is complete, the corresponding area collapses.

Closely related to the changes in the mucosa of the bronchi are the changes in the mucosa of the nose and sinuses. The nasal sinuses are involved in a high percentage of all patients with asthma. The nasal quality of the voice, the irregular obstruction, the rhinorrhea and then the presence of polypi and the findings of sinuses dull on transillumination and in roentgenograms present a combination which goes with a story of chronic persistent asthma to make a clinical picture which is characteristic. The nature of the sinus disturbance is not clear. Evidence of a local infection is not always present—the pathologic picture is one of edema with eosinophilia and round cell infiltration (chronic inflammation of a special sort), and, as Weille⁷³ has shown, the trouble in any one sinus is capable of clearing without local treatment to that particular sinus. Presumably, the sinusitis represents a special form of “allergic reaction.” Cameron⁷⁴ agrees with this theory. It may depend on some variety of chronic nerve stimulation and consequent overactivity of the mucous membrane, as Phillips⁷⁵ has suggested in a paper entitled “The Fifth, Ninth and Tenth Nerves in Bronchial Asthma.” Lasowsky and his associates⁷⁶ describe “hyperergic inflammation in tissues” during brief stimulation of nerves. Cooke and Grove⁷⁷ show that the incidence of sinusitis increases with the increase of age at the time of onset. In 92 per cent of 248 cases of infective asthma it was an etiologic factor. In the authors’ hands operative treatment gave good results in 70 per cent of 120 patients.

73 Weille, Francis L. Studies in Asthma. XVIII. The Surgical Treatment of Chronic Sinusitis in Asthma, *J. A. M. A.* **100** 241 (Jan 28) 1933.

74 Cameron, J. A. M. Part Played by Allergy or Sensitization as Factor in Predisposing Mucous Membrane of Nasal Passages and Paranasal Sinuses to Infection and Its Bearing upon Treatment of Disease of These Cavities, *J. Laryng. & Otol.* **50** 493, 1935.

75 Phillips, K. The Fifth, Ninth and Tenth Nerves in Bronchial Asthma, *Ann. Otol., Rhin. & Laryng.* **45** 373, 1936.

76 Lasowsky, J. M., Wyropajew, D. N., and Jurmann, M. N. Hyperergic Inflammation in Tissues During Brief Stimulation of Nerves, *Virchows Arch. f. path. Anat.* **295** 334, 1935.

77 Cooke, R. A., and Grove, R. C. Relation of Asthma to Sinusitis, with Special Reference to the Results from Surgical Treatment, *Arch. Int. Med.* **56** 779 (Oct.) 1935.

Weille⁷⁸ has had an extensive experience in the problem of the relation between the nose and throat and the asthma. A study of his end-results shows that of 100 sinus operations, ultimate cure was obtained in only 10 patients, although another 55 were markedly benefited. Tonsillectomy was performed on 36 patients—one was “cured,” and in 24 the condition was improved. The extraction of abscessed teeth gave better results. Of 59 patients, 3 were “cured” and 36 were benefited. These particular results are long term results. A few patients were followed for only six months but about four fifths of them were followed for at least a year, and two fifths were followed for over three years. The figures are disturbing, perhaps, but it must be remembered that treatment of this sort is directed at the result of a disease process and not at its cause.

An interesting novelty is the suggestion by Moruzzi⁷⁹ that asthma be treated by injecting the patient's serum into the nasal mucosa in daily doses of from 0.2 up to 1 cc. He treated 11 patients in this way—3 were relieved and 4 improved (he does not say how long they were followed up).

Cardiac Asthma—Cardiac asthma is discussed by Ernestene and Knowlton⁸⁰. The seizure usually depends on a sudden failure of the left ventricle, so common in older persons with advanced arteriosclerosis. Cardiac asthma may, however, occur also in younger persons who have mitral stenosis and then suffer a sudden increase in the heart rate and in the pulmonary congestion. Venesection as a mode of therapy deserves more attention.

It is a pleasure to read the report of Conybeare and Witts,⁸¹ which emphasizes the changing character of asthma, the many different factors which enter into the cause of the attack and the recovery from it and, consequently, the ever present difficulty of determining the effect of treatment with true accuracy.

Specific Treatment of Asthma—The specific treatment of asthma has received scant attention. Closely related, however, is the article by Fantus and Feinberg⁸² on the therapy of reactions to horse serum,

78 Weille, Francis L. Studies in Asthma. XIX. The Nose and Throat in Five Hundred Cases of Asthma, *New England J. Med.* **215** 235, 1936.

79 Moruzzi, D. Intramucous Autoserum Therapy for Bronchial Asthma, *Polislinico (sez. prat.)* **42** 905, 1935.

80 Ernestene, A. C., and Knowlton, R. S. Cardiac Asthma, *Ohio State M. J.* **32** 717, 1936.

81 Conybeare, E. T., and Witts, L. J. A Criterion for the Treatment of Asthma, *Guy's Hosp.* **85** 138, 1935.

82 Fantus, Bernard, and Feinberg, S. M. The Therapy of (Horse) Serum Reactions. General Rules in the Administration of Therapeutic Serums, *J. A. M. A.* **107** 1717 (Nov. 21) 1936.

with the rules governing the administration of therapeutic serum. The technical procedures are explained carefully. A method of oral desensitization to common foods is described by Keston, Waters and Hopkins⁸³ and in their hands has been found to be effective, especially in the treatment of small children with chronic allergic eczema due to hypersensitivity to food. The method consists essentially in a series of increasing daily doses.

Graeser and Rowe⁸⁴ present another article on the inhalation of epinephrine hydrochloride as a method for relief of asthma in children. This is of practical value, as I know from experience. Nowadays the special atomizer and the small bottle of 1:100 solution of epinephrine hydrochloride are put up together by the pharmaceutical house so that the outfit is neat, convenient and not too expensive. It is important, however, that the patient be carefully instructed in its use, for unless the bulb is squeezed at the beginning of inspiration the spray will not be inhaled deeply into the finer bronchi, and good results will not be obtained. Ellsworth and Sherman⁸⁵ describe a case in which the injection of epinephrine in an asthmatic patient resulted in tetany, which developed promptly after the relief of the bronchial spasm. The short interval suggested strongly that hyperventilation made possible by the epinephrine resulted in the washing out of carbon dioxide and the production of alkalosis and, consequently, tetany. The occurrence is another argument against the use of excessive doses of epinephrine. In the ordinary patient such a small quantity as 0.3 cc. of the solution is as effective as a larger amount, which often is followed by disagreeable by-effects, such as shivering, headache, pallor and tachycardia.

Nonspecific Treatment of Asthma—Nonspecific therapy is widely used in asthma. Two important articles, one by Hektoen⁸⁶ and the other by Cecil,⁸⁷ on nonspecific protein therapy in general deserve careful attention. That nonspecific treatment does not act by stimulating the eosinophil cells is shown by Peshkin and Messer,⁸⁸ who found that

83 Keston, B. M., Waters, I., and Hopkins, J. G. Oral Desensitization to Common Foods, *J. Allergy* **6** 431, 1935.

84 Graeser, J. B., and Rowe, A. H. Inhalation of Epinephrine Hydrochloride for Relief of Asthma in Children, *Am. J. Dis. Child.* **52** 92 (July) 1936.

85 Ellsworth, Read, and Sherman, William B. Tetany in an Asthmatic Patient Following the Administration of Epinephrine, *J. A. M. A.* **106** 284 (Jan. 25) 1936.

86 Hektoen, Ludvig. Reactions to Nonspecific Protein Treatment of Infectious Diseases, *J. A. M. A.* **105** 1765 (Nov. 30) 1935.

87 Cecil, Russell L. Nonspecific Protein Therapy, *J. A. M. A.* **105** 1846 (Dec. 7) 1935.

88 Peshkin, M. M., and Messer, William. Asthma in Children. XII. Influence of Specific and Nonspecific Treatment on the Differential Leukocyte Count, with Special Reference to the Eosinophils, *Am. J. Dis. Child.* **50** 1374 (Dec.) 1935.

a venom protein solution, which stimulates the eosinophils more than does milk, is not more effective in cases of asthma in children than are injections of milk

Intractable Asthma—The treatment of intractable asthma is always difficult Balyeat and his associates⁸⁹ have had real success with the intratracheal injection of iodized poppy seed oil in doses of from 5 to 10 cc instilled at intervals of from one to four weeks In 35 of the 50 patients in whom poor results were obtained by allergic management, good results were finally obtained by the use of this method The authors can demonstrate roentgenographically that when the bronchi are filled with a tough, sticky exudate the injected oil works its way below the exudate to float it upward and thus to close off the smaller tubes In this way the mechanical factor dependent on the presence of the sticky mucus is modified Anderson⁹⁰ also has used this method, and he claims that patients who have been treated by intratracheal injection of iodized oil have lost their clinical sensitiveness to former irritants Furthermore, he finds the treatment safe and without danger, either immediate or remote, to the lungs In my experience iodized oil persists for some time in the bronchi, as can be shown by repeated roentgenograms, and no doubt a series of lipoid granulomas are often produced It may be, however, that even if granulomas are formed, they do little harm

Histamine is recommended by Dzsinnich,⁹¹ who gave increasing doses to 15 patients with bronchial asthma and to 3 with urticaria—the maximum dose being 0.01 mg Frequently, ten or twelve injections resulted in complete disappearance of the symptoms

Dorsal sympathectomy has been tried by Levin,⁹² who recommends the destruction of the ramus either by injections of alcohol or by operative removal of the upper portion of the thoracic ganglionated trunk In 75 per cent of 23 patients with severe asthma treated by this method complete relief was obtained

Helium should be, at least theoretically, the ideal means for treating severe asthma The size of the bronchial lumen is reduced by muscular spasm or by the formation of the sticky exudate and plug, and

89 Balyeat, A., Sevler, L. E., and Shoemaker, H. A. The Diagnostic and Therapeutic Use of Iodized Oil in Cases of Intractable Asthma, *Radiology* **24** 303, 1935

90 Anderson, William. The Treatment of Bronchial Asthma by Intratracheal Injections of Iodized Oil, *New York State J. Med.* **36** 1151, 1936

91 Dzsinnich, A. Histamine in Treatment of Allergic Conditions (Bronchial Asthma and Urticaria), *Klin. Wchnschr.* **14** 1612, 1935

92 Levin, G. L. L. The Treatment of Bronchial Asthma by Dorsal Sympathectomy, Direct and Indirect (Use of Alcohol), *Ann. Surg.* **102** 161, 1935

anything which will increase the flow of air past the obstruction is to be recommended. A. L. Barach⁹³ who originated the method of using helium deserves great credit. In two new articles, illustrated by pictures and diagrams, he describes new refinements in the technic and the results of new studies on the physiologic effects and the clinical end-results. Briefly these include decreases in the pulmonary ventilation, in the pulmonary pressure and in the length of expiration.

Prognosis—The prognosis in asthma is generally good. Studies of end-results in patients with clinical allergy are conspicuous by their absence and it is gratifying to find a paper by Leon Unger⁹⁴ on the results of treatment in 207 cases after a period of from one to thirteen years. Forty-five of his patients were "cured," and 104 were greatly improved. The figure of 21 per cent is interesting, because it is practically the same as the figure which I obtained in a follow-up of 1,074 patients in 1928. If other physicians whose methods of treatment are so well described would employ the same yardstick, the comparative results would be interesting and instructive.

Witts⁹⁵ considers the prognosis in asthma in an article which is along general lines and is full of common sense, but he does not present figures to define the end-results exactly.

FCZI MA

Sulzberger⁹⁶ has published several papers on the varieties of dermatologic allergy, discussing at the same time the problems of nomenclature and classification and more recently the medicolegal aspects. The patient who becomes sensitive to some occupational dust has two difficulties. First, his work has brought him into contact with the substance and the employer appears liable, but, second, he alone out of many other workers has shown symptoms—he has a constitutional sus-

93 Barach, A. L. Use of Helium in Treatment of Asthma and Obstructive Lesions in Larynx and Trachea, *Ann Int Med* **9** 739, 1935, The Effects of Inhalation of Helium Mixed with Oxygen on the Mechanics of Respiration, *J Clin Investigation* **15** 47, 1936.

94 Unger, Leon. Bronchial Asthma. Results of Treatment in Two Hundred and Seven Patients Under Observation for a Period Varying from One to Thirteen Years, *J Allergy* **7** 364, 1936.

95 Witts, L. J. Prognosis in Asthma, *Lancet* **1** 273, 1936.

96 Sulzberger, M. B., and Goodman, Joseph. Nomenclature, Definition and Classification of Allergy and Allergic Manifestations, *M Rec* **143** 17, 1936, Remarks on Definition and Classification in Certain Forms of Dermatologic Allergy, *New England J Med* **215** 330, 1936, The Relative Importance of Specific Skin Hypersensitivity in Adult Atopic Dermatitis, *J A M A* **106** 1000 (March 21) 1936, Medico-Legal Aspects of Occupational Dermatoses, *Am J Surg* **30** 531, 1935. Sulzberger¹

ceptibility, which is allergy, and for this the employer is not liable. In legal medicine the problem is real and is not limited necessarily to the cutaneous manifestations of clinical allergy.

A number of articles concern interesting cases. Brunsting and Williams⁹⁷ have collected the reports of 48 patients with ragweed dermatitis. Caulfeild⁹⁸ describes tulip fingers. Biederman⁹⁹ studied a truck driver who was sensitive to gasoline. The relation between his work and the occurrence of dermatitis was clearcut, and when he was tested by placing one arm over the open mouth of a bottle of gasoline, itching, redness and later blisters developed on the exposed sites, the reaction continuing for from twenty-four to forty-eight hours. A similar test on the doctor's arm gave negative results. Grolnick¹⁰⁰ has written two articles on the question of dermatitis due to adhesive plaster, describing the substitutes for adhesive plaster which can be used in making a patch test. Bonnevie and Genner¹⁰¹ add a report of another patient with eczema due to the dyes in clothing. Hoffman and Rattner¹⁰² found two children in whom eczema was caused by cod liver oil. Sulzberger¹⁰³ finds that itch mites of canary birds can cause dermatitis in human beings.

In all these cases the diagnosis depended primarily on the intelligent taking of the history, which suggested the proper selection of substances to be tested by the patch method.

Meantime, Field and Sulzberger¹⁰⁴ describe a patient who was evidently sensitized by the cutaneous tests. The fact indicates that the discrepancy of results may sometimes depend on the development of sensitiveness during the period of study.

97 Brunsting, Louis A., and Williams, Donald H. Ragweed (Contact) Dermatitis, *J A M A* **106** 1533 (May 2) 1936.

98 Caulfeild, A H W. "Tulip Fingers," Ragweed Dermatitis, *Canad M A J* **34** 506, 1936.

99 Biederman, Joseph B. A Case of Contact Dermatitis Produced at a Distance, *J A M A* **106** 2236 (June 27) 1936.

100 Grolnick, M. Studies in Contact Dermatitis. I Adhesive Plaster Dermatitis, *Technics for Surface Testing on Patients Sensitive to Adhesive Plaster*, *J Allergy* **7** 341, 1936, II Adhesive Plaster Dermatitis. Clinical and Immunologic Observations on Patients Sensitive to Adhesive Plaster, *ibid* **7** 556, 1936.

101 Bonnevie, P., and Genner, V. Eczema Due to Dyed Clothing, *Arch Dermat & Syph* **34** 220 (Aug.) 1936.

102 Hoffman, S I., and Rattner, H. Infantile Eczema from Cod Liver Oil. Report of Two Cases, *J A M A* **107** 494 (Aug 15) 1936.

103 Sulzberger, M B., and Kaminstem, I. Avian Itch Mites as a Cause of Human Dermatoses. Canary Birds' Mites Responsible for Two Groups of Cases in New York, *Arch Dermat & Syph* **33** 60 (Jan.) 1936.

104 Field, Hans, and Sulzberger, M B. Experiments in Poison Ivy Sensitivity, *J Allergy* **7** 139, 1936.

FUNGI IN ALLERGY

Dermatologists have been greatly interested in the new approach to the diagnosis of diseases of the skin which the advance in the knowledge of allergy and of fungi has opened up in the last few years. Swartz¹⁰⁵ presents the essentials of the classification of fungi in his general article on their rôle in medicine. Pennington¹⁰⁶ has analyzed 155 cases of allergic dermatitis and found that sensitivity to fungi was involved in about 60 per cent and was the sole cause of trouble in 30 per cent. Thirty-three patients were treated with doses of fungus extract given intracutaneously. Of these, 21 were cured and another 6 were definitely improved. In some cases, however, other methods of treatment, including removal of test-positive substances, were employed.

A certain type of eczema depends on a specific cause which is carried to the skin by the blood stream. In this type the method by which the offending substance reaches the blood makes little difference. For example, in a child with typical infantile eczema, egg is absorbed from the gastro-intestinal tract. In other cases the allergen may be absorbed by inhalation through the lungs. Dust can cause eczema which, like hay fever and asthma, may come and go with changes in environment. The new knowledge of fungus spores in the air and their relation to inhalant allergy of all sorts is of practical importance. An increase in the knowledge of molds will be desirable.

Lamson and Rogers¹⁰⁷ found that 12 per cent of 1,259 patients with asthma and hay fever showed a positive reaction to cutaneous tests with molds, while Feinberg¹⁰⁸ found that 28 per cent of his patients with asthma and hay fever reacted to molds. In another paper Feinberg¹⁰⁹ presents charts showing the daily incidence of mold spores in the air and the relation between their number and the occurrence of symptoms in his patients. Underwood¹¹⁰ has found that, even if molds are not the primary cause of trouble, an additional sensitiveness to them can make a bad condition worse.

105 Swartz, J. H. The Rôle of Fungi in Medicine, *New England J. Med.* **215** 322, 1936.

106 Pennington, Edna S. An Evaluation of the Relative Role of Fungi (Trichophyton) and Other Allergens in Patients with Allergic Dermatoses, *South M. J.* **29** 407, 1936, Trichophyton and Monilia Extracts in Allergic Dermatoses, *J. Allergy* **7**:54, 1935.

107 Lamson, Robert W., and Rogers, Erving L. Skin Hypersensitivity to Molds, *J. Allergy* **7** 582, 1936.

108 Feinberg, S. M. Mold Allergy. Its Importance in Asthma and Hay Fever, *Wisconsin M. J.* **34** 254, 1935.

109 Feinberg, S. M., and Little, H. T. Studies on the Relation of Micro-organisms to Allergy, *J. Allergy* **7** 149, 1936.

110 Underwood, G. R. Importance of Fungus (*Alternaria*) as Cause in Nebraska, *Nebraska M. J.* **20** 400, 1935.

The former observations of Cohen¹¹¹ have been confirmed by Wagner and myself¹¹² and the importance of fungi in their effect on various environmental substances is being better understood. When fibers of cotton or kapok which are new and unused are extracted, the fluid gives positive results to cutaneous tests in only a few patients. When, on the other hand, extracts are made of old, used material, a large proportion of the cutaneous reactions are found to be positive. That this change depends chiefly on the activity of fungi which grow on the vegetable fiber is shown in various ways. Conant, Wagner and myself¹¹³ found numerous fungi in cultures of the stuffing in pillows, mattresses and furniture. Brown¹¹⁴ filled flasks with new cotton fiber and then inoculated them with mold cultures. Cutaneous tests with extracts of the resulting mixture, however, gave negative results. My colleagues and I have made a similar study, which will be presented soon. We shall show, first, that sterilization by steam pressure of new vegetable fiber hinders the growth of molds on the fiber and, second, that the choice of molds is important, because whereas certain molds will grow well on certain substrates these same molds will not grow well on other substrates. In our experience it is possible to produce a good growth of molds in flasks full of new material and to show that after a time extracts of this growth often produce positive reactions in cutaneous tests. This new knowledge is of practical importance because the list of patients in whom asthma has been completely relieved by simple changes in bedding and furniture is considerable. In the meantime, that cutaneous tests made with fungus extracts are often associated with reagins has been demonstrated by Persons and Martin¹¹⁵ and also by Cazort¹¹⁶.

URTICARIA

Hopkins and Kesten¹¹⁷ have made a useful and practical list and classification of the varieties of urticaria, differentiating between acute and chronic forms and their causes, as well as between localized and

111 Cohen, Milton B. Observations on the Nature of the House Dust Allergens, *J Allergy* **6** 517, 1935

112 Wagner, Harold C., and Rackemann, F. M. Kapok, *J Allergy* **7** 224, 1936

113 Conant, N. F., Wagner, Harold C., and Rackemann, F. M. Fungi Found in Pillows, Mattresses and Furniture, *J Allergy* **7** 234, 1936

114 Brown, Grafton T. Hypersensitiveness to Fungi, *J Allergy* **7** 455, 1936

115 Persons, E. L., and Martin, D. S. Passive Transfer Antibodies for Skin Saprophytic Fungi in a Patient with Superficial Scaling Dermatitis, *J Clin Investigation* **15** 429, 1936

116 Cazort, A. G. The House Dust Antigen in Allergy, *South M J* **29** 1022, 1936

117 Hopkins, J. G. and Kesten, B. M. Urticaria. Etiologic Observations, *Arch Dermat & Syph* **29** 358 (March) 1934

generalized lesions. They recognize that in this, as in other varieties of allergy, the offending substance to which the patient is hypersensitive may enter the body through the respiratory tract and be distributed by the blood. In another group of patients the disease seemed to depend on a focus of infection, and the authors consider that urticaria from this cause may occur even in patients who have not an allergic predisposition.

DRUG ALLERGY

Drug allergy is receiving more and more attention, and clinicians are becoming aware of its increasing frequency. In considering the chemistry of hypersensitiveness, it was pointed out that those substances which are relatively unstable and which therefore, combine easily with protein are also those substances to which a specific sensitiveness is often acquired. Perhaps it is for this reason that the modern development of many new drugs has sometimes led to trouble.

Benjamin and Biederman¹¹⁸ describe a patient in whom agranulocytic leukopenia developed following the use of novaldin, which is a close relative of aminopyrine. Strauss¹¹⁹ describes a patient who took a single tablet of peralga (another form of aminopyrine) and in whom collapse and severe asthma developed. Dinitrophenol caused asthma in a patient reported on by Noun¹²⁰. Dameschek and Colmes¹²¹ demonstrate a strongly positive cutaneous reaction when aminopyrine was mixed with protein (blood serum) and the mixture was used for a scratch test. Lichtenstein and Stillians¹²² report the case of a young man with tuberculosis who received six intravenous injections of gold sodium thiosulfate and in whom exfoliative dermatitis developed which persisted for several months. Hudson¹²³ has described purpura haemorrhagica as due to a sensitiveness to compounds of gold and arsenic. During the illness patch tests with gold sodium sulfate gave positive results. Other patients with similar though less severe dermatitis also showed a positive reaction to a patch test with the drug.

118 Benjamin, J. E., and Biederman, J. B. Agranulocytic Leukopenia Induced by a Drug Related to Aminopyrine, *J. A. M. A.* **107** 493 (Aug. 15) 1936.

119 Strauss, M. G. Allergy to Amidopyrine. Blood Studies Following Anaphylactic-Like Shock in a Patient, *New England J. Med.* **215** 177, 1936.

120 Noun, M. H. Asthma from Dinitrophenol Sensitization (Case), *J. Iowa M. Soc.* **25** 610, 1935.

121 Dameschek, William, and Colmes, A. The Effect of Drugs in the Production of Agranulocytosis, with Particular Reference to Amidopyrine Hypersensitivity, *J. Clin. Investigation* **15** 85, 1936.

122 Lichtenstein, M. R., and Stillians, A. W. Results of Patch Tests with Gold Sodium Thiosulphate, *Arch. Dermat. & Syph.* **31** 758 (May) 1935.

123 Hudson, E. G. Purpura Hemorrhagica Caused by Gold and Arsenical Compounds, *Lancet* **2** 74, 1935.

Martinaud¹²⁴ observed a patient who had a fatal attack of asthma during an attempt to produce local anesthesia of the nose with a solution of butyn

Hypersensitiveness to substances of simple chemical structure may, however, occur Gelfand¹²⁵ reports on a patient who was hypersensitive to arsenic and in whom marked generalized dermatitis developed after the application of a hair tonic and dandruff remover Settle¹²⁶ had a patient who took two tablets of quinine sulfate and the next day had inflammatory lesions on the palms and on the tongue

As Hunter¹²⁷ pointed out in his inclusive review of the literature published in 1935, there is, in almost all of these cases, a history of three distinct circumstances First, the drug was taken for a considerable period without difficulty Second, there was another considerable period during which the drug was not taken, and then, third, symptoms occurred promptly when the drug was taken again after the interval In these cases there are sensitization and incubation that are entirely comparable to the anaphylaxis experiment

Other special cases are described Card¹²⁸ had a patient who worked in a chromium-plating factory and it was found that an attack could be provoked by the injection of 4 mg of potassium dichromate Parlato¹²⁹ studied a nun who had corneal ulcers caused by sensitiveness to the sachets used in the church vestments She gave a marked reaction to cutaneous tests with orris powder The frequency with which patients show a positive reaction to cutaneous tests with extracts of human tissues is described in an interesting paper by Simon and Ryder,¹³⁰ who found that extract of pituitary caused a reaction in a small percentage of subjects

124 Martinaud, M Fatal Attack of Asthma During Local Anesthesia by Washing Nasal Mucosa with Solution of Butyn Case, *Anesth et analg* **1** 199, 1935

125 Gelfand, H Harold Hypersensitiveness to Arsenic Dermatitis from Liquid Arvon, *J Allergy* **7** 254, 1936

126 Settle, R O Dermatitis Medicamentosa Due to Quinine, *J A M A* **106** 1801 (May 23) 1936

127 Hunter, F T Agranulocytosis, *New England J Med* **213** 663, 1935
Kracke, R R, and Parker, F P The Relationship of Drug Therapy to Agranulocytosis, *J A M A* **105** 960 (Sept 21) 1935

128 Card, W Ingram A Case of Asthma Sensitivity to Chromates, *Lancet* **2** 1348, 1935

129 Parlato, Salvatore, J Corneal Ulcers Due to a Common Allergen, *Arch Ophth* **14** 587 (Oct) 1935

130 Simon, Frank A, and Ryder, C F Hypersensitiveness to Pituitary Extracts *J A M A* **106** 512 (Feb 15) 1936

OTHER SYMPTOMS OF ALLERGY

Foster Kennedy¹³¹ has listed a number of neurologic disturbances which may be attributable to allergy. Certain convulsive states and some forms of retrobulbar neuritis are in the list, as well as migraine. More interesting are the cases in which paralysis of certain nerves occurs after doses of foreign serum and perhaps represents a certain special form of serum disease. Hemiplegia has been described in this connection, and another patient with urticaria suffered a migrating type of paralysis which seemed to follow a migrating type of edema.

In close accord is the case report by Cutter,¹³² of San Francisco, concerning a boy of 14 who stepped on a rusty nail in a barnyard. Three weeks later he visited a physician because of twitchings in various muscle groups for one day and inability to open his jaw. Within forty-eight hours he was given 125,000 units of tetanus antitoxin. Five days later he was given 15,000 units. After that increasing deafness developed with noises in the ears and double vision. The symptoms lasted for about a month. It is surprising perhaps that this treatment with foreign serum given at the intervals stated did not result in an even more vital reaction.

Migraine—Migraine is still a difficult problem. Some light has been thrown on its mechanism by Goltman,¹³³ who observed a young woman with headache severe enough to require cerebral exploration. Through a burr opening Goltman could observe that during the aura there was spasm of the cerebral vessels, but with the onset of the headache he could see vascular dilatation develop, with edema of the brain. The clinical aspects of migraine are well described in a paper by Gordon¹³⁴ who points out that allergy can be demonstrated as an important factor in only a relatively small proportion of cases. The treatment of migraine with ergotamine tartrate has been advocated and pursued by Lennox.¹³⁵ His recent experiences with the drug in 120 cases are presented. Relief from an attack was obtained in 107 cases.

Other Symptom Complexes—Other complexes have been described as having an allergic basis—gout by Pasteur Vallery-Radot,¹³⁶ articular

131 Kennedy, Foster. Allergic Manifestations in the Nervous System, *Tr Am Neurol A* **61** 49, 1935.

132 Cutter, Richard D. Auditory Nerve Involvement After Tetanus Antitoxin. First Reported Case, *J A M A* **106** 1006 (March 21) 1936.

133 Goltman, A. M. The Mechanism of Migraine, *J Allergy* **7** 351, 1936.

134 Gordon, A. H. A Clinical Lecture on Migraine, *New England J Med* **213** 1017, 1935.

135 Lennox, W. G., and von Storch, T. J. C. Experience with Ergotamine Tartrate in One hundred and Twenty Patients with Migraine, *J A M A* **105** 169 (July 20) 1935.

136 Vallery-Radot, P., and Mauric, G. Gout and allergie, *Progrès med* Oct 12, 1935, p 1631.

disease by Wellisch¹³⁷ and disorders of the gastro-intestinal tract, liver and gallbladder by Urbach¹³⁸, but in none of the cases does the evidence for an allergic cause rest on a firm foundation. On the other hand, Lewin and Taub¹³⁹ describe a patient subject to recurrent attacks of synovitis which seemed to be due to the ingestion of English walnuts. Cohen¹⁴⁰ mentions periarteritis nodosa, having made the diagnosis in 2 cases of asthma before death occurred. He writes "The diagnosis is not difficult if the clinician will watch for symptoms and signs which may be explained on the basis of a temporary or permanent blood supply to any organ."

SUMMARY

The problems to which I referred in the review of two years ago are not yet solved. The function and purpose of the allergic reaction are being studied, and some attempt is being made to apply the results of laboratory experiments to patients, but there is still a long way to go. The increased understanding of tissue reactions is a step forward. Concerning the allergic subject, it is not yet clear that his variation from the normal depends on anything more than a quantitative change. Fortunately, however, the students of allergy are paying more attention to the patient as a whole. Studies of metabolism, of hormones and of food factors have been begun. Precise information on the mechanism of the production of symptoms, however, is still lacking. Surely there must be some reason for the prostration and illness associated with chronic intractable asthma. The whole subject is fascinating, partly because the field is large and the problems diverse and partly because any important results will lead to the benefit of a large number of persons who really suffer.

263 Beacon Street

137 Wellisch, E. Allergic Components in Diseases of Joints, *Wien med Wchnschr* **85** 935, 1935.

138 Urbach, E. Allergic Disorders of Gastro-Intestinal Tract, Liver and Gallbladder, *Rev méd-chir d mal du foie* **11** 116, 1936.

139 Lewin, Philip, and Taub, Samuel J. Allergic Synovitis Due to Ingestion of English Walnuts, *J A M A* **106** 2144 (June 20) 1936.

140 Cohen, M. B., Kline, B. S., and Young, A. M. The Clinical Diagnosis of Periarteritis Nodosa, *J A M A* **107** 1555 (Nov 7) 1936.

Book Reviews

By-Effects in Salvarsan Therapy and Their Prevention. By Dr V Genner
Price, 22 kroner Pp 360 Copenhagen Levin & Munksgaard, 1936

This monograph compiled from the experience of the University Clinic of Dermato-venereology, at Copenhagen, assembles a mass of clinical data regarding arsenic intoxication during the treatment of syphilis. The entire subject, of course, is of great interest and has been widely studied, it must have been tedious work to gather together the very extensive literature which is reviewed, to assemble it properly and to add observations regarding it.

First there is discussed the theoretical basis for arsenic intoxication, then there follow chapters on arsphenamine erythema, jaundice, albuminuria and what the author calls "paratherapeutic joint complaints." These chapters lead to a discussion as to how such uncomfortable by-effects of arsphenamine therapy may be avoided, especially by the use of a concentrated dextrose solution as a solvent for the arsphenamine. Finally the author pleads for individualization of anti-syphilitic treatment, for, he claims, it is possible before treatment is begun to determine whether a patient is intolerant to arsphenamine and to plan a suitable individualized treatment so that he can receive adequate therapy without serious or permanent injury.

On the whole, the material of the book is well digested, so that the monograph should be useful as a work of reference not only to syphilographers but also to all clinicians who administer the various arsenicals.

Aparato respiratorio By Doctores F Martinez and Isaac Berconsky Pp 283
Buenos Aires Ed Atenco, 1936

This volume is an interesting and complete treatise on the respiratory system. It is in actuality a work on physical findings, in which the authors thoroughly cover the anatomy, physiology and pathology of the respiratory system, including the topography of the chest. In their volume they consider the mediastinum, pleura and diaphragm in separate chapters.

The printing is on excellent paper, and the entire contents are profusely illustrated with exceptionally clear figures. The chapters on topography and physical examination of the thorax are especially commendable. There is an excellently illustrated chapter on radiology.

In undertaking a work of this kind, the authors have succeeded in eliminating a large majority of the obsolete signs to which a work on physical diagnosis seems to be heir. The volume lends itself readily to teaching purposes. It is unfortunate that there is not a chapter on the heart and the great vessels.

Treatment in General Practice The Management of Some Major Medical Disorders [Articles Reprinted from the British Medical Journal]
Price, \$3.50 Pp 260, with 6 illustrations New York Paul B Hoeber, Inc., 1936

This series of articles on treatment arouses no enthusiasm in the reviewer. The discussion is superficial, full of outworn "practical" advice and burdened with complicated, old-fashioned and obviously impotent prescriptions. The reviewer parted company with the views expressed in the first section on influenza, where the statement is made that "a free current of air is probably the most important single point in the whole treatment." The advice to give a vaccine of pneumococci, streptococci and influenza bacilli in the treatment of lobar pneumonia and

the reasons in favor of this procedure are out of accord with sound practice, and so it goes throughout the book. Better discussions can be found in any reputable textbook.

Lésions du pancréas et troubles fonctionnels pancréatiques By Marc Bolgert. Price, 45 francs. Pp 262, with 22 illustrations. Paris: Masson & Cie, 1935.

This is an interesting monograph on pancreatic disease. It is concerned especially with the method of testing the external secretion of the gland as collected by a duodenal tube after the injection of purified secretin. There is a great deal of interesting detailed material, for a complete account of which the original work must be consulted.

Gefässerweiternde Stoffe der Gewebe By J. H. Gaddum and H. H. Dale. Price, 18 marks. Pp 200. Leipzig: Georg Thieme, 1936.

This is a systematic discussion of the chemical, pharmacologic and physiologic bearings of "vaso-dilator tissue substances"—histamine, acetylcholine and other substances. The subject matter is concentrated and heavily documented, this makes difficult consecutive reading, but the book is invaluable as a work of reference.

Books Received

THE THEORETICAL POSSIBILITY OF IMMUNIZING THE OLFACTORY MUCOSA AGAINST POLIOMYELITIS VIRUS By S. Peskind, M.D. Paper. Pp 22. Cleveland: S. P. Mount Printing Co., 1936.

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DIABETIC COMA

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BOSTON

The conquest of diabetic coma is in sight. During 1929 and 1930 in Stettin, Germany, with a population of 270,000, there was not a single death from diabetic coma.¹ Boston cannot make so good a showing, but the following letter from the health commissioner of the city speaks for itself.

March 31, 1936

My dear Dr. Joslin:

I am happy to report to you that in the City of Boston during 1935 there was not a death from any cause whatsoever in a diabetic under nineteen years of age. During this twelve month period there were in all 288 deaths classified as diabetes and I understand including those with diabetes as a secondary cause 301 deaths.

Yours very truly,

(Signed) William B. Keck, M.D.
Health Commissioner

In this twelfth paper on diabetic coma we shall (1) present 42 new cases, bringing to 318 the total number of patients treated since 1923, (2) discuss various considerations for the classification of cases of coma which will allow a better comparison of treatment by different methods, (3) describe in detail 3 fatal cases—in 1 the condition was mistaken for insulin shock and no insulin was given, death taking place three hours after the patient was admitted to the hospital, and in the other 2 death occurred from infections eight and twenty days, respectively, after recovery from the coma, (4) report on the respiratory metabolism in a case of diabetic coma, and, finally, (5) compare the results of our methods of treatment of diabetic coma in 54 children.

From the George F. Baker Clinic, Elliott P. Joslin, M.D., medical director, at the New England Deaconess Hospital.

1. Gottschalk, A. Das Stettiner System der Diabetikernachsorge, Klin. Wchnschr. 10:704 (April 11) 1931.

entering the hospital with a carbon dioxide-combining power of the venous plasma of 15 volumes per cent or less, with 1 death (19 per cent mortality), with the results of treatment with methods recently proposed in this journal by Hartmann,² who reported on 27 patients with an initial plasma carbon dioxide content of 15 volumes per cent or less, with 5 deaths, or an 18.5 per cent mortality, and 15 patients (of the 27) treated with sodium lactate, with 2 deaths, or a 13.3 per cent mortality

FORTY-TWO NEW CASES OF COMA

To the 276 cases of coma reported by us³ between 1923 and October 1934 we now add 42 cases⁴ in 41 patients treated in the fifteen months between Oct 6, 1934, and Jan 1, 1936. Six of the patients have been considered as "coma offenders" in our previously published series. In table 1 are recorded in detail the data regarding the 42 cases and in table 2 a summary of this and the preceding six series.

The average age in the present series was 28.2 years. The oldest patient was 66.5, and the youngest was 2.4 years of age. Twenty-seven of the patients were females and 15 males. The preponderance of coma in females has been consistent in each series. It has already been pointed out that this occurs in the ages in which the preponderance of cases of diabetes is in males. It is theoretically possible that hyperactivity of the pituitary gland during catamenia or during pregnancy may account for this. Thus, 6 women of our entire series of patients with coma, including 2 in the present group, had the attack during pregnancy.

The average duration of diabetes prior to the onset of coma was five and three-fifths years. The average sugar content of the blood when the patient was admitted to the hospital was 0.54 per cent, and this had fallen to 0.2 per cent on the second and to 0.19 per cent on the third day. In 3 of this series of 42 patients the initial sugar value was over 1,000 mg per hundred cubic centimeters of blood. Two of the 3 patients (cases 13 and 38) recovered. The average carbon dioxide-combining power of the plasma was 11 volumes per cent. It rose to 30 volumes per cent on the second and 41 volumes per cent on the third day. In 11 patients the carbon dioxide-combining power of the plasma at the time of the patient's admission to the hospital was less than

2 Hartmann, A. F. Treatment of Severe Diabetic Acidosis, *Arch Int Med* **56** 413 (Sept) 1935. See table 1 on page 415 for data for 12 patients with a plasma carbon dioxide content of 15 volumes per cent or less and for 3 others mentioned in footnote 1, page 414 (patients treated with sodium lactate).

3 Marble, A., Root, H. F., and White, P. Diabetic Coma, *New England J Med* **212** 288 (Feb 14) 1935. See this article for earlier references.

4 One case was not included, although the carbon dioxide-combining power was 19 volumes per cent, because the urine was sugar-free, owing to treatment in another hospital before transfer to us.

TABLE 1—Data for Forty-two Consecutive Cases of Diabetic Coma

Case No	Age at Time of Onset of Coma, Years	Date, 1934	Clinical Data		Blood			Urine		Nonprotein Nitrogen, Mgr per 100 Cc	Urine		Insulin Units	Comment and Result
					Sugar, %	Plasma CO ₂ Combining Power, Vol %		At Entrance	Sugar, %		After In Urine, Hours			
			1	2		1	2					1		
1	35.2	Oct 6	+	D	0.57	3	0	18	13	230	120	115	Thyroid storm	
2	39.1	Oct. 15	+	D	0.82	2	1	28	11	410	60	64		
3	14.3	Oct. 16	+	D	0.63	8	15	18	9	185	70	67		
4	2.9	Oct. 23	+	D	0.10	2		6.0	13	111	10	2		
5	27.5	Nov. 3	0	C	0.37	19		1.0	15	65	54	64		
6	50.2	Nov. 8	+	C	0.33	11	42	3.0	8	225	66	52		
7	15.0	Nov. 10	+	C	0.60	11	25	3.3	5	205	110	70	Pulmonary tuberculosis	
8	49.4	Nov. 18	+	C	0.42	10	70	3.8	13	110	63	75		
9	13.7	Dec. 2	+	C	0.07	20	17	2.5	7 1/2	115	70	76		
10	31.2	Dec. 11	+	C	0.16	6	30	1.1	3	120	75	60		
11	48.5	Dec. 24	+	D	0.29	34	37	3.3	12	315	60	64		
12	13.9	Dec. 30	+	U	0.26	1	18	3.1	4	190	85	70		
13	19.3	1935 Jan 7	+	U	0.51	1	35	1.1	11 1/2	515	55	110		
14	16.2	Jan 8	+	C	0.06	<1	30	1.1	6.0	200	100	32		
15	4.6	Jan 8	+	C	0.02	1	30	6.1	6.1	515	55	110		
16	33.7	Jan 8	+	C	0.25	16	30	0.9	0.9	120	100	95	Labor and pneumonia fatal	
17	15.3	Jan 9	+	C	0.19	8	29	3.6	3.6	90	70	60		
18	27	Feb 9	+	C	0.33	15	31	+	+	111	15	36		
19	39.8	March 3	+	D	0.16	11	29	5.1	5.1	285	75	70		
20	2.4	March 5	+	C	0.18	6		5.6	5.6	16	10	12		
21	32.7	March 13	+	C	0.07	17	39	+	+	80	49	40		
22	6.6	April 5	+	C	0.44	9		+	+	78	36	34		
23	34.8	April 19	+	C	0.53	10		+	+	270	65	40		
24	14.1	April 29	0	C	0.22	18		0.6	0.6	110	66	70	Pregnancy	
25	65.6	July 8	+	U	0.38	7		+	+	270	65	40		
26	37.4	July 9	+	D	0.26	21	46	+	+	480	40	30		
27	18.1	July 21	+	D	0.18	23		2.3	2.3	270	54	46		
28	15.2	July 22	+	D	0.16	12	34	2.4	2.4	19	430	55		
29	13.2	July 22	+	C	0.17	15		2.4	2.4	120	70	62		
30	7.3	Aug. 3	+	D	0.23	17	20	+	+	70	54	52		
31	4.5	Aug. 14	+	C	0.13	2	30	+	+	220	154	46		
32	8.7	Aug. 29	+	D	0.06	6	21	+	+	66	32	14		
33	12.4	Sept. 9	+	C	0.25	19	45	+	+	120	52	46	Fatal	
34	42.5	Sept. 19	+	U	0.37	2		0	0	130	60	60		
35	20.0	Oct. 4	+	C	0.06	15	41	+	+	200	35	55		
36	33.7	Oct. 10	+	SO	0.40	13	28	2.3	2.3	138	52	84		
37	47.8	Oct. 12	+	D	0.17	18	27	2.8	2.8	400	20	50		
38	32.8	Nov. 3	+	SO	0.05	12	20	+	+	265	30	60		
39	24.3	Nov. 8	+	D	0.21	13	35	+	+	510	105	80		
40	30.0	Nov. 8	+	SO	0.11	4	19	3.9	3.9	170	45	57		
41	35.9	Nov. 25	+	C	0.26	18	38	5.0	5.0	210	36	64		
42	43.0	Dec. 13	+	C	0.33	14	44	+	+	155	70	72		
43	13.8	Dec. 18	+	C	0.47	16	34	4.8	4.8	245	180	135	Fatal	
44	7.5	Dec. 18	+	C	0.36	17	23	2.7	2.7	130	60	60		
45	57.2	Dec. 20	+	U	0.27	17	23	2.7	2.7	200	35	55		

* U indicates unconsciousness, with the patient unresponsive even to strong stimuli, S-C, stupor, with the patient responsive to strong stimuli, D, drowsiness and stupor, C, consciousness, with the patient in most instances, however, somewhat clouded mentally

TABLE 2—Comparative Data, by Averages, for Seven Series of Cases of Diabetic Coma

Series	Num ber of Cases	At tack Time of Coma, Years	Dur a tion of Diabetes Mellitus, Years	Blood												Insulin, Units			Fatal Cases	
				Sugar, %	Carbon Dioxide Combining Power of Plasma, Vol %			Non protein Nitrogen, Mg per 100 Cc	Urine at Entrance											
					Day	Day	Day		Day	Directie Acid	Sugar, %									
												1	2	1	2	3	1	2	3	
1	24	31.5 (24)	2.4 (24)	0.47 (23)	0.20 (20)	15 (24)	33 (20)	31 (10)	47 (16)	++ (24)	3.3 (24)	154 (24)	63 (22)	58 (21)	5	21				
March 1923																				
2	28	31.6 (28)	2.8 (28)	0.49 (28)	0.20 (20)	14 (28)	29 (20)	30 (10)	46 (21)	++ (28)	3.4 (28)	166 (28)	59 (26)	49 (26)	1	11				
April 1925 to Feb 1927																				
3	53	29.1 (53)	1.0 (53)	0.53 (52)	0.21 (46)	13 (53)	28 (37)	38 (12)	60 (33)	++ (53)	3.1 (53)	183 (53)	40 (50)	39 (50)	5	9				
March 1927 to Feb 1929																				
4	74	31.3 (74)	3.5 (74)	0.49 (74)	0.20 (51)	11 (73)	29 (42)	35 (13)	48 (52)	++ (74)	3.7 (74)	252 (74)	49 (65)	41 (62)	13	18				
Feb 1929 to Aug 1931																				
5	42	26.1 (42)	3.5 (42)	0.47 (42)	0.15 (37)	12 (20)	28 (28)	33 (5)	37 (17)	++ (42)	3.9 (40)	201 (42)	51 (41)	45 (39)	2	5				
Aug 1931 to Oct 1932																				
6	53	28.5 (55)	1.3 (55)	0.51 (55)	0.17 (46)	12 (55)	29 (31)	34 (9)	49 (28)	++ (54)	3.6 (54)	196 (55)	52 (51)	44 (50)	6	11				
Oct 1932 to Oct 1934																				
7	42	28.2 (42)	5.6 (42)	0.54 (42)	0.20 (39)	11 (42)	30 (34)	41 (5)	49 (18)	++ (42)	3.7 (42)	210 (41)	66 (41)	61 (41)	3	7				
Oct 1934 to Jan 1936																				

* The figures in parentheses indicate the number of determinations on which the average was computed for each series

5 volumes per cent. Ten of the 11 recovered. It should be noted that the chemical values on the second and third days are for only a partial number of the entire series, often these values are not determined, since many patients recover so rapidly that later determinations seem needless. Possibly this fact was overlooked by Hartmann, who, on page 429 of his paper, stated that "a number of his [Joslin's] patients still had marked acidosis on the second and third days of treatment."

The nonprotein nitrogen content of the blood when the patient was admitted to the hospital was more than 40 mg per hundred cubic centimeters of blood for 12 of the 18 patients for whom the test was performed and 70 mg per hundred cubic centimeters or more for 3.

The average of insulin prescribed in the first twenty-four hours of treatment was 210 units.

Dietary indiscretion was the most common etiologic factor, occurring in 12 cases. Five patients had omitted taking insulin. Four had not kept to their diet and had omitted insulin. In 7 cases infection was the inducing factor. Eight patients had unrecognized or inadequately treated diabetes, and in 2 the cause of coma was unexplained. In 4 cases the condition appeared to have been precipitated by endocrine complications. Thus, 1 patient (case 1) had combined "thyroid storm" and diabetic coma. She entered a surgical service of the hospital. The sugar content of the blood was 0.12 per cent, and the urine contained 2 per cent sugar at 7 p. m. At 7 the next morning the sugar content of the blood was 0.57 per cent, and the carbon dioxide-combining power was 3 volumes per cent. Two patients were pregnant, and the pregnancy in 1 was complicated by lobar pneumonia. She was delivered normally of a nonviable infant. The other (case 22) had early toxemia of pregnancy, and the uterus was emptied at the ninth week. One child (case 23) entered in coma with the onset of her first catamenial period.

Eighteen of the patients belonged to our juvenile series (*onset of diabetes at 15 years of age and under*). This increases the number of patients in coma in the juvenile series to 134 treated since 1923, of these 133 recovered. Among 1,000 patients in whom the onset of diabetes was at the age of 15 years or earlier, a recent tabulation⁵ showed that 300 had coma at some time in the course. This series included cases in which the disease developed in the preinsulin era, however, and of the last 400 patients seen, only 46 had had coma at some time in their diabetic life.

Clinical Considerations—Only 4 of the 42 patients were totally unconscious. Kussmaul breathing was present in all but 2 patients.

⁵ White, P., in Joslin, Elliott P. *The Treatment of Diabetes Mellitus*, ed. 5, Philadelphia, Lea & Febiger, 1935, p. 509.

Diacetic acid was not present in the urine of 3 patients who had advanced acidosis and signs of renal block

Complications—In 10 patients complications included "thyroid storm," pregnancy and pneumonia, toxemia of pregnancy, pulmonary tuberculosis, otitis media, prostatic abscess, acute tonsillitis, severe varicella and acute infection of the upper respiratory tract

Mortality—The mortality rate in the present series was 7.1 per cent. The mortality rate for our 318 cases was 11.9 per cent (38 deaths). The age of the patient has a direct influence on mortality, as will be discussed later.

CLASSIFICATION OF CASES OF DIABETIC COMA

No one would think of comparing the results of treatment for pneumonia in patients above 60 years of age in one city with those in patients

TABLE 3—*Data on the Rise in Mortality with the Advance in Ages of Patients in Diabetic Coma*

Age at Coma, by Decades	Total Number of Cases	Fatal Cases	
		Number	Percentage
First	23	0	0.0
Second	123	3	2.4
Third	38	3	8.0
Fourth	43	5	11.6
Fifth	33	7	18.4
Sixth	33	14	42.4
Seventh	16	5	31.3
Eighth	4	1	25.0
Total	318	38	11.9

less than 15 years of age in another city. The same applies to diabetic coma. The mortality among old persons with diabetic coma is high, but among 54 children (15 years of age or less at the time of coma) there has been but 1 death. Consequently, in any report on diabetic coma the treatment should be compared on the basis of age, and advice with regard to treatment should be based on experience with patients of different ages. Table 3 illustrates the general rise in mortality for coma from 0 in the first decade and 2.4 per cent in the second to 42.4 per cent in the sixth. Old age by no means invariably implies a fatal outcome, however. On Jan. 29, 1936, a woman, not included in this series, recovered from coma at 75 years of age, being two years older than our oldest patient previously recorded. The blood sugar value at the time of her admission to the hospital was 0.66 per cent, and the carbon dioxide-combining power of the plasma was 12 volumes per cent.

Without some criterion as to the extent of the acidosis it is impossible to compare different methods of treatment. In 1917, five years

before the introduction of insulin, one of us⁶ reported on 15 patients in diabetic coma who recovered after showing a carbon dioxide tension of the alveolar air of 20 mm of mercury or less. The carbon dioxide-combining power of the plasma of these patients ranged between 14 and 28 volumes per cent. These facts led to the use of a tension of the carbon dioxide of the alveolar air of 20 mm of mercury and later a carbon dioxide-combining power of the plasma of 20 volumes per cent as an arbitrary dividing line between cases of precoma and cases of coma. The latter figure still remains a good point of division. In 9 of 91 patients in coma in our series with a carbon dioxide-combining power of the plasma between 16 and 20 volumes per cent, inclusive, death occurred. The mortality, 10 per cent, was about the same as for the entire series, and to exclude these 91 cases would result in the omission of some patients who were in serious acidosis. One might decide to omit cases in which there was a carbon dioxide-combining power of over 15 volumes per cent in order to stiffen the requirements. However, a carbon dioxide-combining power of 18 or 20 volumes per cent and a carbon dioxide content of 15 volumes per cent are nearly comparable values. Certainly the exclusion of cases in which the carbon dioxide-combining power was between 16 and 20 volumes per cent would exclude many fatalities, therefore, we hold to our present standard.

If there is any more accurate or better method of determining the depth of coma than the determination of the carbon dioxide-combining power or content of the blood plasma, certainly all should adopt it. We cannot accept the blood sugar or the nonprotein nitrogen content or the degree of glycosuria as an index, and the blood pressure is not distinctive enough. Unconsciousness is difficult to measure, depending as it does a good deal on the effort taken to arouse the patient. Therefore, it cannot be used as a set standard, although a record of the degree of unconsciousness should be made. So, too, the Kussmaul respiration varies in different stages. The longer the diabetic coma lasts, the less distinctive becomes the Kussmaul respiration, and during the last few hours before death it usually disappears.

THREE DEATHS IN COMA

1 *Diabetic Coma Mistaken for Hypoglycemia*—A man (case 32) who was almost 29, a tea taster, learned that he had diabetes and began treatment on May 25, 1922. Fortunately for him he had married a nurse the preceding year. When he first consulted one of us (Dr. E. P. Joslin) seven months later, in January 1923, his weight when dressed was 111 pounds (50.5 Kg), or about 42 pounds (19.1 Kg) below the standard weight for his age and height. After his marriage his weight had risen to its maximum of 135 pounds (61.4 Kg) at the onset of diabetes. At

6 Joslin, E. P. Diabetes. The Results of Past Treatment and Future Problems, Bull. Johns Hopkins Hosp. 29:82 (April) 1918.

first no history of diabetes was obtained, but later in an uncle and a cousin the disease developed. In January 1923 except for emaciation the physical examination revealed no abnormality. The Wassermann reaction was negative. The sugar content of the blood was 0.25 per cent (250 mg), and the urine contained 2 per cent sugar. The urine became sugar-free with a low diet, and insulin treatment was begun within a few months. In 1924 the patient's weight had risen to 122 pounds (55.5 Kg). He reported infrequently, and although he worked steadily and his weight rose to 127 pounds (57.7 Kg) on Jan 7, 1929, on a diet of 46 Gm of carbohydrate, 74 Gm of protein and 167 Gm of fat, it was only with considerable insistence on our part that the carbohydrate of his diet was increased to 76 Gm. The dosage of insulin was 12, 0 and 12 units. The blood pressure was 96 systolic and 70 diastolic. On Jan 17, 1933, his weight (dressed) was 131 pounds (59.5 Kg). The urine showed diacetic acid, one specimen contained 2.7 and another 0.6 per cent of sugar. The blood sugar content was 0.24 per cent (240 mg), the nonprotein nitrogen content 33 mg and the cholesterol content 234 mg per hundred cubic centimeters. The diet which he had been following contained 102 Gm of carbohydrate, 77 Gm of protein and 155 Gm of fat. The dosage of insulin was 32 units a day. The blood pressure was 90 systolic and 60 diastolic. Two years intervened until his next visit on Jan 15, 1934, his last before he entered the hospital eight months later. His weight (dressed) was 136 pounds (61.8 Kg). The urine contained 2.3 per cent of sugar. The blood sugar content was 0.22 per cent (220 mg) four hours after lunch, and the cholesterol value was 238 mg per hundred cubic centimeters. The blood pressure was 112 systolic and 70 diastolic. The heart was normal except for a soft systolic murmur. Slight radial sclerosis was noted.

On Sept 19, 1935, at 10 50 p m, the patient, a methodical, upright man, who was punctilious about his diet and insulin treatment, was admitted to the New England Deaconess Hospital unconscious and pulseless. Two days before he had gone on a business trip to New York, the first without his wife in the thirteen years he had had diabetes. After completing his business he took the afternoon train for Boston, and just before the train reached that city he became unconscious. From the train he was taken in an ambulance first to a suburban police station, 8 miles distant, and from there to his home, and then was brought to the hospital.

Although when the patient was admitted to the hospital the radial pulse could not be felt, a possible systolic blood pressure of 70 mm was obtained. The heart rate was slow and regular, and the sounds were distant and of poor quality. The skin was cold, and the rectal temperature was 97 F (36.1 C). The respiration was regular, slow and labored. Nine grams of dextrose was given intravenously in 50 per cent solution at 11 05 and again at 11 20 p m. His color improved, but the respiratory and pulse rates did not. At 11 30 and again at 11 40 p m, 1 cc of epinephrine hydrochloride, 1:1,000, was given subcutaneously, with some elevation of the pulse rate. The patient moved a little. Nine grams more of dextrose was given intravenously at 11 55 p m. The respiration then became more rapid and less labored. At 12 20 a m he apparently recognized his wife. At 12 30 he was taking water from a spoon, and between 12 30 and 12 45 he swallowed 100 cc of orange juice. His color was improving, but he continued groaning. At 1 a m, though pulseless, he responded to 0.23 Gm of caffeine with sodium benzoate. At 2 a m he died.

The gross observations at autopsy were acute dilatation and marked congestion of the stomach, and congestion of the lungs, with slight edema and fatty infiltration of the liver. Microscopic study confirmed the previous diagnosis, with the addition of subacute pancreatitis, deposition of glycogen in the nuclei of the hepatic

cells and in the renal tubules, fatty degeneration of the kidneys and hemorrhagic necrosis of the gastric mucosa. It is notable that the vessels of the heart were smooth and elastic, there were no emboli or thrombi. The aorta was normal, except for a slight degree of atheromatous degeneration in the abdominal portion. Yet this man had lived for thirteen years on a diet comparatively low in carbohydrate.

At the time of the patient's entrance to the hospital the blood sugar content was 1.23 per cent (1,230 mg), the nonprotein nitrogen content was 100 mg per hundred cubic centimeters and the two samples of blood plasma, pooled, showed a carbon dioxide-combining power of 2 volumes per cent. The fact that these extreme values were not known until after death occurred does not ease one's conscience that the patient died while being treated for hypoglycemia instead of diabetic coma. The blood sugar value of 1,230 mg did not necessarily imply a poor prognosis because we have noted 13 cases with 8 recoveries in which the blood sugar values were 1,000 mg per hundred cubic centimeters or above when the patient was admitted. Dillon and Dyer⁷ have recently reported 16 cases of diabetic coma in which the blood sugar content was 1,000 mg or more when the patient was admitted to a ward of the metabolic department of the Philadelphia General Hospital. Five of the patients recovered and 11 died. In Hartmann's⁸ recent series of 91 (86 and 5) cases in children no case was mentioned in which the blood sugar value was over 922 mg. Only 27 had values for the carbon dioxide-combining power of 15 volumes per cent or less, yet 5 died. The nonprotein nitrogen content was 100 mg per hundred cubic centimeters, but we have seen recovery in 3 of 7 cases in which the value was equal to or higher than that. It is true that the carbon dioxide-combining power was only 2 volumes per cent, yet in 9 cases in which there was such a value we have had 7 recoveries. The low blood pressure did not justify death. Consequently, in this case the condition was not clinically or chemically hopeless.

Urine was not obtained until at autopsy. It contained 1.5 per cent sugar and acetone but no aceto-acetic acid. Even if urine had been obtained when the patient was admitted to the hospital it would not have solved the differential diagnosis between coma and hypoglycemia, because often the first specimen of urine voided by the hypoglycemic patient contains sugar, having been secreted perhaps hours earlier by the kidneys.

Reasons for the Wrong Diagnosis. This patient was admitted to a floor of a hospital where at least 200 patients in diabetic coma have been treated in ten years. He was accompanied by his wife, a nurse

7 Dillon, E. S., and Dyer, W. W. Diabetic Coma with Extreme Hyperglycemia, *Am J M Sc* **190** 683 (Nov.) 1935.

8 Hartmann,² p. 418, table 3, p. 414, footnote.

He was promptly seen by a doctor, house officers and a night supervisor, who together must have observed at least 50 and probably 100 patients in coma, but all were so positive that this patient had hypoglycemia that they broke every rule and did not secure instant chemical verification of the diagnosis. Although a specimen of blood was taken at once and again one and one-half hours later, the report was delayed, in spite of the fact that we have arrangements by which examinations of blood can be made any time in the twenty-four hours. No urine was obtained, partly because the patient could not void and partly because of hesitancy in cases of coma in catheterizing a patient, due to the fact that infection of the genito-urinary tract is so common among diabetic patients.

If in a hospital to which more than 1,200 diabetic patients are admitted a year and which prides itself on its treatment of coma, such an error can occur, it is reasonable to infer that it may occur in other hospitals. An unconscious diabetic patient in any hospital must be surrounded with facilities, including personnel and methods, which will insure prompt chemical aids to diagnosis day or night. There must be a "coma-drill," just as much as a fire-drill. Substitute house officers must be examined for their ability to perform laboratory analyses in an emergency at night, and no matter how clearly correct the diagnosis and treatment may seem to younger doctors or house officers, their superiors must be informed and full responsibility assumed by them.

The fact that this patient had not been seen for eight months likewise should not be overlooked. A diabetic patient if he wishes to live should keep in touch with his physician. It is true that in 12.5 per cent of our last 981 fatal cases (up to March 13, 1935) the patient had lived for twenty years after the onset of diabetes. But this shows how careful one must be to follow up cases if one wishes to improve the percentage of survivals. This patient had had diabetes for thirteen years. He had at least moderately severe involvement. In the course of five years he had reported to us for examination only three times. A diabetic patient should report to his doctor at least every three months. This man had had reactions, and on his trip to New York he may have reduced the dosage of insulin to avoid them. However, if he had been more conversant with present methods of diet and treatment, he possibly would have averted an attack of coma. The diabetic patient must keep in touch with his physician. Physicians should not hesitate to follow up their patients who have had diabetes for a long time, even though sometimes it exposes them to criticism.

2 *Fatal Coma Precipitated by Infection in the Genito-Urinary Tract*—A man (case 17) who was 63 at the onset of diabetes in June 1932, entered the New England Deaconess Hospital on Feb 9, 1935. For three days he had complained of constipation, increasing weakness and deep breathing. At the time of the

patient's admission to the hospital respiration of the Kussmaul type was present, and his breath had an acetone odor. The blood pressure was 140 systolic and 68 diastolic. The blood sugar content was 0.44 per cent, and the carbon dioxide-combining power of the venous plasma was 15 volumes per cent. The urine contained 3.8 per cent sugar, 2 plus diacetic acid and a slight trace of albumin. The sediment was filled with white blood corpuscles. The prostate gland was enlarged and boggy. A partial intestinal obstruction developed, and a mass could be felt low down in the abdomen. He was relieved of diabetic acidosis easily with 52 units of insulin. However, the evidences of pelvic and renal infection with metastatic infection in the lungs precluded any surgical treatment. The nonprotein nitrogen content of the blood steadily rose and finally reached 105 mg per hundred cubic centimeters, and the patient died eight days after entrance to the hospital. At autopsy large prostatic and periprostatic abscesses, with induration and inflammation of the tissue about the bladder, were present. Bilateral pyelonephritis with abscess formation and one perinephric abscess as well as nephrolithiasis and acute hemorrhagic and suppurative cystitis completed the involvement of the genito-urinary tract. The pancreas weighed 80 Gm, many islands were partially hyalinized. Incidental observations included pulmonary abscesses, bronchopneumonia and a diverticulum of the duodenum. (Since the first report of 2 cases of duodenal diverticulum in diabetic patients by Thorning and Root,⁹ 10 other cases have been discovered.)

The frequency and severity of genito-urinary infections in diabetic patients have not been appreciated generally. In 35 of 196 (18 per cent) autopsies at the New England Deaconess Hospital infection of the urinary tract of a serious nature was present.¹⁰ Hematogenous infection usually due to a streptococcus or a staphylococcus, was present in 25 cases. Ascending infection, usually associated with some type of obstruction, such as calculi or prostatic hypertrophy, was present in 5 cases, and in the remaining 5, including cases of pyelonephritis and renal abscesses, the origin could not be determined.

Three of these 35 patients had diabetic coma with a reduction in the carbon dioxide-combining power of the plasma to below 20 volumes per cent, and 4 had severe acidosis. The presence of ketone bodies in large amount had not seemed to exert any favorable influence in retarding the bacterial growth. Indeed, it is generally true that ketosis in a diabetic patient is associated with lowering of the resistance to infection. In these cases it appeared that genito-urinary infection had been present before the acidosis was recognized and that if it exerted any influence, it was in the direction of diminishing the resistance to the infection.

In diabetic patients infection with *Bacillus coli* is a serious menace, especially in older patients confined to bed by reason of a surgical operation. Paralysis of the bladder leads to back pressure and ascending infection. *B. coli* thrives at a p_H of from 6 to 7, according to Schohl

9 Thorning, W. B., Jr., and Root, H. F. Diverticula of the Duodenum and Diabetes, *Am J Digest Dis & Nutrition* **2** 17 (March) 1935.

10 Sharkey, T. P., and Root, H. F. Infection of the Urinary Tract in Diabetes, *J A M A* **104** 2231 (June 22) 1935.

and Janney,¹¹ but is inhibited at a p_H of from 4.6 to 5 and from 9.2 to 9.6. Possibly other factors are of greater importance when the diabetes is not under good control. Richardson¹² found that, regardless of the level of the blood sugar, the bactericidal property of the whole blood of diabetic patients was weaker than that of nondiabetic patients. Furthermore, after inoculation with typhoid vaccine a diabetic patient is less able to form agglutinins. Richardson suggested that this lowered resistance was due chiefly to a disordered state of cellular nutrition related to the diminished glycogen reserves. A lowered opsonin-producing power of diabetic blood has been reported by Horster¹³ in depancreatized animals. Certainly the frequency and the insidious, often "silent" character of such infections in diabetic patients, especially in those with acidosis, is to be borne in mind constantly.

3 The Third Fatal Case in the Present Series and the Relation of the Condition to Trauma—An American housewife (case 42) aged 58 entered the Deaconess Hospital on Dec 20, 1935, in diabetic coma. The onset of diabetes was in May 1925. Diabetic coma in 1930 and a subsequent carbuncle had been treated successfully. In July 1935 a blister appeared on the end of the third right toe, and drainage from this area continued for several weeks, while the patient was not under our care.

The present illness began with a fall down four stairs on Dec 16, 1935, when the patient twisted her right knee. The injury seemed at the time to be slight. She got up and did her usual work for that entire day. Alternate hot and cold applications were employed, not because of pain but to "prevent trouble." On the next day, however, the patient suddenly felt such severe pain in the knee that a physician who was called in gave morphine. A day later swelling of the leg and pain came on which prevented movement, and the patient was put to bed with the leg in an open cast.

Difficult breathing developed on about December 19, and on December 20 the patient entered the hospital in diabetic coma, with a carbon dioxide-combining power of the plasma of 17 volumes per cent and a blood sugar content of 0.42 per cent. The eyeballs were soft. The patient was not entirely unresponsive but was delirious and uncooperative. With 225 units of insulin and the usual treatment with gastric lavage and liquids, given both subcutaneously and intravenously, she made a good recovery.

On December 22 the third right toe was found to have become infected about and under a callus. The right knee was much swollen, as if fluid were present, and the presence of fluid was confirmed by roentgen examination. There was

11 Schohl and Janney, quoted by Clark, A. *Escherichia Coli Bacilluria Under Ketogenic Treatment*, Proc Staff Meet, Mayo Clin **6** 605 (Oct 14) 1931.

12 Richardson, R. *Immunity in Diabetes. I Influence of Diabetes on Development of Antibacterial Properties in Blood*, J Clin Investigation **12** 1143 (Nov) 1933, *II Relative Importance of Nutritional State and of Blood Sugar Level in Influencing Development of the Agglutinin After Typhoid Vaccine*, *ibid* **14** 389 (July) 1935.

13 Horster, H. *Beitrag zur Klarung der Ursache der verminderten Widerstandsfähigkeit des zuckerkranken Organismus gegen Infektion*, Deutsches Arch f klin Med **176** 502 (July 9) 1934.

edema of the lower part of the leg but no evidence of lymphangitis. A blood culture was taken because of an afternoon fever, but no growth was obtained. Daily examinations of the patient were made in the search for a cause for the persistent afternoon rise in temperature, ranging to 100 or 101 F, and a leukocyte count of 19,000. On December 29 the entire right leg was swollen, and the right thigh was definitely larger than the left. At this time it did not seem that the infectious process in the knee accounted for the fever. There had been no break in the skin at the knee joint. The condition was thought to be due to phlebitis. A localized area of tenderness developed on the anterior aspect of the lower third of the thigh. On January 5 crepitus was felt in the knee joint, suggesting the presence of gas due to infection.

On January 7 purulent fluid was aspirated both from the knee joint and from the thigh. *Streptococcus haemolyticus* was grown from the fluid from both areas. About 6-15 that same evening the patient became faint, and her appearance was anxious. A black stool was passed the next day, but this was discounted as she had been receiving iron by mouth.

A blood transfusion of 750 cc was given on January 8. On January 9 incision and drainage of the right thigh and knee joint were made so that the entire thigh was laid open. The joint capsule was observed to be destroyed by direct extension of infection from the knee joint into the thigh. The patient died at 8 o'clock in the evening, twenty days after recovery from diabetic coma.

The postmortem anatomic diagnosis was as follows: duodenal ulcer of large size in the first portion of the duodenum, with an artery projecting directly into the ulcer, much changed blood in the intestine, indicating a recent hemorrhage, many diverticula of the jejunum, healed appendicitis, fibrous adhesions of the cecum, and septic infection of the right knee and thigh. The pancreas weighed 60 Gm and showed diffuse fibrosis and hyalinization of the islands of Langerhans. Fatty infiltration was abundant, and some lymphocytic infiltration was present.

THE RESPIRATORY METABOLISM IN DIABETIC COMA AND THE CARBON DIOXIDE CONTENT OF THE BLOOD

Among the many metabolic changes occurring in the patient suffering from advanced diabetic coma, certain features stand out with special prominence. One may here include the total energy exchange, changes in the body temperature with their effect on energy exchange, dehydration, changes in the base concentration of the blood and tissues consequent to vomiting and polyuria, changes in the chemical components of the blood and urine, the production of ketone bodies and their excretion through the lung and kidneys and changes in the function of the kidney. In the following case report data bearing on certain of these points will be presented.

A boy (case 38), aged 17 years, was found on Feb 23, 1923, to have diabetes. He was first seen by us on March 8, at which time the urine contained 0.1 per cent sugar. He left the hospital in two weeks, taking 5 units of insulin three times a day, with a diet which included 158 Gm of carbohydrate, 75 Gm of protein and 120 Gm of fat. At this time his net weight was 147 pounds (66.8 Kg). On Oct 4, 1927, the urine contained 0.3 per cent sugar. The patient was taking a diet of 91 Gm of carbohydrate, 78 Gm of protein and 138 Gm of fat. The blood sugar value was 0.26 per cent. The dose of insulin was 20 units in the morning and 20

units before supper In April 1929 a roentgenogram of the lungs showed a suspicious increase in the markings, but no definite diagnosis of tuberculosis was possible

About Nov 1, 1935, a rash broke out rather suddenly over the patient's face, scalp, trunk and extremities He had had some acne previously During the next week he felt rather weak and could not work, he remained at home On November 7 difficulty in breathing and vomiting developed The patient entered the Deaconess Hospital on November 8, at about 3 30 p m, in profound diabetic coma, although he was not entirely unresponsive to strong stimuli

At this time the blood pressure was approximately 80 systolic and 42 diastolic The pulse rate was 108 The respiration was of the Kussmaul type The eyeballs

TABLE 4—*Data on the Analyses of the Blood in Case 38 During Severe Diabetic Coma*

Date	Hours	Blood Sugar, Mg per 100 Cc	Carbon Dioxide Combining Power of Venous Plasma Vol %	Nonprotein Nitrogen, Mg per 100 Cc
11/ 8/35	3 30 p m	1,068	4	70
	4 30 p m		8	
	5 35 p m	1,050		
	7 30 p m	690	14	
	10 30 p m	580	19	
11/ 9/35	7 30 a m	110		
11/11/35	7 30 a m	50	58	33

TABLE 5—*Results of Analyses of Urine in Case 38 During Severe Diabetic Coma*

Date, 1935	Volume, Cc	Sugar, %	Diabetic Acid	Acetone	Ammonia (Calculated as Ammonia), Gm	Nitrogen, Gm
Nov 8, admission specimen	240	3.9	0	0	0.14	0.59
Nov 8 and 9, 15 hour specimen	1,350	2.5	0		1.16	9.70
Nov 11 and 12, 24 hour specimen	1,850	0.4	0		3.80	

were so soft that even three hours later, after 1,500 cc of physiologic solution of sodium chloride and over 200 units of insulin had been administered, Prof J H Waite could not measure the tension of the eyeballs with a tonometer The patient's hands and feet were extremely cold The entire trunk, face, arms and scalp were spotted with superficial crusted lesions and pustules, later diagnosed as varicella Incidentally, varicella developed in the patient's daughter a few days later A few râles were heard in the lungs, but later roentgenograms showed no parenchymal involvement Analyses of the blood and urine, with a summary of the treatment given, are detailed in tables 4 and 5 Treatment consisted of the administration of 220 units of insulin within the first hour and a total of 430 units during the first five hours (see table 6) Physiologic solution of sodium chloride was given subcutaneously and intravenously Gastric lavage was performed

The subsequent course in the hospital was entirely uneventful The patient left the hospital on November 26, on a diet of 171 Gm of carbohydrate, 114 Gm of

protein and 121 Gm of fat, making a total of 2,229 calories. His weight was 135 pounds (61 Kg), in contrast to 127 pounds (58 Kg) at the time of his admission to the hospital. The dosage of insulin was 24 units before breakfast, 8 units at noon, 24 units before supper and 8 units at midnight. On this regimen the urine was free from sugar.

The total energy exchange is usually increased in the early stages of diabetic coma. Contributing to this effect are undoubtedly the extra exertion involved in the deep respiration and the restlessness of the patient, as well as the direct effect of the acidosis. This was observed in the cases studied by one of us¹⁴ at the Carnegie Nutrition Laboratory and was also shown in a case of coma (case 36) studied at the Deaconess Hospital shortly before the case under discussion. In this early stage there is no fall in the body temperature. However, as acidosis advances and exhaustion comes on with dehydration, the body temperature falls, and in this stage there may be a change in the total energy exchange.

TABLE 6—*Treatment in Case 38 During Severe Diabetic Coma*

Hours After Admission	Insulin, Units	Saline Solution	
		Intravenous, Cc	Subcutaneous, Cc
1	220		1,500
2	40	750	
3	40		
4	90		
5	40		
8-11	80	750	1,500

In order to study this point, we were able, through the courtesy of Dr. Francis G. Benedict and Dr. Thorne Carpenter, of the Carnegie Nutrition Laboratory, to observe the oxygen exchange of the aforementioned patient by means of the helmet apparatus devised by Dr. Benedict. With this apparatus no nose clips or mouth piece are necessary, and with a patient thoroughly relaxed in deep coma, no struggling or other complicating factors enter in. The results obtained for the oxygen consumption in this case are shown in table 7.

At 4:45 p. m. on November 8, when the patient was apparently dying and the rectal temperature was low, the oxygen consumption was lower than it was five hours later, when after treatment the rectal temperature had risen. After the patient's recovery from acidosis the basal metabolism fell again to a level of 1,536 calories on November 25. The lower value of oxygen absorption at the height of coma, even though it was still higher than the level obtained later, after complete recovery, tends to support the view that the low body temperature in

¹⁴ Joslin, E. P. *Diabetic Metabolism with High and Low Diets*, Washington, D. C., Carnegie Institution of Washington, 1923, pp. 158-160.

diabetic coma is not due merely to loss of heat through the evaporation of water but is really due to a depression of heat production, which is directly proportional to the length and severity of the acidosis. However, these are merely preliminary observations, awaiting further study before conclusions can be drawn.

Another evidence of the severity of diabetic coma is the character of the respiration. In the early stages of diabetic coma the respiration may be extraordinarily regular, even though deep. However, when exhaustion sets in and the body temperature falls, the character of the respiration may continue to be deep but may become irregular. In case 38 the tracings of the respiratory rate showed a considerable variation, although this did not interfere with an accurate determination of the oxygen consumption. The rate varied from 35 to 40 a minute. This rate steadily fell and four hours later was 25 per minute.

Renal function is of fundamental importance in the early stages of diabetic acidosis and also later, as it is often the determining factor in

TABLE 7—*Oxygen Absorption per Minute in Case 38 During and Subsequent to Diabetic Coma*

Date, 1935	Hour	Oxygen Absorbed per Minute, Cc	Temperature, F
Nov 8	4 45 p m	286	96.0 (rectal)
Nov 8	9 45 p m	385	99.0 (rectal)
Nov 9	8 00 p m	317	99.0 (rectal)
Nov 16	8 00 a m	300	97.8 (by mouth)
Nov 25	8 00 a m	275	98.0 (by mouth)

recovery. In the foregoing case, a specimen of urine obtained by catheter was free from diacetic acid and acetone. The total amount of ammonia was 0.14 Gm., and in this same specimen the total urinary nitrogen content was 0.59 Gm., making the ammonia nitrogen-total nitrogen ratio 19 per cent. During the next eighteen hours the urine contained only 1.16 Gm. of ammonia, and the total nitrogen content was 9.7 Gm., giving a still lower ammonia nitrogen-total nitrogen ratio of 9.9 per cent. This extraordinarily low rate of ammonia formation indicated a marked impairment of renal function and a marked diminution in the process of ammonia formation within the kidneys.^{14a} In some cases of diabetic acidosis Goodall and one of us¹⁵ found ammonia values as high as 5.2 Gm. in twenty-four hours and an ammonia nitrogen-total nitrogen ratio up to 39 per cent. Another evidence of impairment of the renal function is the fact that the nonprotein nitrogen content of the blood

^{14a} Another interpretation would be that there was sufficient alkali in the body and no necessity to utilize this mechanism.

¹⁵ Goodall, H. W., and Joslin, E. P. The Clinical Value of the Estimation of Ammonia in Diabetes, Boston M. J. **158**: 646 (May) 1908.

was 70 mg per hundred cubic centimeters. Furthermore, it is worth noting that although the specimen of urine contained no diacetic acid or acetone, a qualitative test for acetone performed on the blood plasma showed a maximal amount of acetone present. The concentration of chloride in the urine was at a minimum. The first catheter specimen of urine contained 0.2 Gm of sodium chloride, or a concentration of 0.08 per cent. This, again, is an index of the degree of dehydration as well as of poor renal function, indicating a late stage of acidosis.

In keeping with these results obtained from the urine, the blood showed a sugar concentration of 1,068 mg per hundred cubic centimeters. This concentration was rapidly reduced with the use of insulin, the patient receiving about 100 units per hour during the first three hours of treatment and a total of 510 units in the first eleven hours.

For this discussion the most important of the analyses of the blood was that of the carbon dioxide-combining power of the venous plasma.¹⁶ The value obtained was 4 volumes per cent. It should be remembered that the low value of 4 volumes per cent for the carbon dioxide-combining power represents the bicarbonate concentration of the separated plasma equilibrated with 5.5 per cent carbon dioxide (alveolar air) at room temperature. The carbon dioxide content of venous plasma, i. e., the concentration of bicarbonate plus dissolved carbon dioxide, amounted to 8.5 volumes per cent about one hour after the patient's admission to the hospital and after 150 units of insulin had been administered and was determined by Prof. A. B. Hastings. Dr. John Talbot, of the Massachusetts General Hospital, analyzed arterial blood about one and a half hours after the patient's admission to the hospital, when 1,500 cc

16 The carbon dioxide-combining power of the venous plasma of our patients in coma has been determined under the direction of Miss Hazel Hunt, formerly the private assistant of Prof. Otto Folin, by the method of Van Slyke and Cullen (*J. Biol. Chem.* **30** 289, 1917), except that the apparatus used has a specially designed pipet with a scale-bearing portion about two and one-half times the length of the standard apparatus. This has enabled us to read low values more accurately. Of our 318 patients in coma, 36 have shown the carbon dioxide-combining power of the plasma as determined by this method to be 5 volumes per cent or less, in fact, 9 have had values as low as 2 volumes per cent. In criticizing values as low as these Hartmann (Hartmann,² p. 429, footnote 8) overlooked the fact that when one uses the table of Van Slyke and Cullen (*J. Biol. Chem.* **30** 344, 1917) to calculate the carbon dioxide-combining power, one automatically makes allowance for physically dissolved carbon dioxide. While this method may not give as accurate an indication of the acid-base balance of the blood as do determinations of the hydrogen ion concentration and of the carbon dioxide content of blood drawn anaerobically, it is convenient and practical for clinical laboratories and "gives results practically as valid as determinations of carbon dioxide on anaerobically separated plasma," according to Peters and Van Slyke (*Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 251).

of physiologic solution of sodium chloride subcutaneously and 220 units of insulin had been administered. This arterial blood had a carbon dioxide content of 5.3 volumes per cent.

The increase in the carbon dioxide-combining power of the blood was steady so that within seven hours on November 8 the value had risen to 19 volumes per cent. On November 11 the carbon dioxide-combining power of the venous plasma was 58 volumes per cent. The use of sodium lactate in racemic mixture has been suggested.¹⁷ Two articles by Prof. Graham Lusk¹⁸ on the effect of lactic acid on the metabolism give some data on its effect when given to dogs.

Lusk added sodium bicarbonate in certain of his experiments so that he was practically giving sodium lactate to the dog. It is not possible to see from the data which he gave that the addition of sodium bicarbonate, bringing about practically a solution of sodium lactate, made any difference in the results of the metabolic studies. If anything, the sodium lactate gave slightly lower results, but it is questionable whether the differences are significant. Apparently the sodium lactate had no more influence on the metabolic rate of these animals than dextrose would have had.

Hartmann¹⁹ stated that racemic sodium lactate given in amounts equivalent to 7 cc. of molar solution per kilogram of body weight produces an increase of 25 to 50 per cent in the oxygen consumption when injected intravenously in normal human subjects, and he said that a similar effect probably occurs in the diabetic patient. Indeed, he attributed the intense hyperpyrexia in 1 of his cases of fatal diabetic coma to this cause. Therefore he recommends a sixth-molar solution of racemic sodium lactate in amounts equivalent to 1 Gm. of sodium bicarbonate per kilogram of body weight. He maintained that this large amount may safely be given without danger of alkalosis, because the sodium lactate must first be metabolized before it is converted into sodium bicarbonate. Such metabolism requires from two to four hours.²⁰ In a case of advanced coma death might occur before the solution of sodium lactate was metabolized.

Actually the dose amounts to 60 cc. per kilogram of body weight, or 3,600 cc. of sixth-molar concentration for a man weighing 133 pounds (60 Kg.). It would be of value to see the respiratory data for a patient in advanced diabetic coma so treated. We have already obtained the solution and if we find it of value we will report on it.

¹⁷ Hartmann,² p. 434.

¹⁸ Atkinson, H. V., and Lusk, G. The Influence of Lactic Acid upon Metabolism, *J. Biol. Chem.* **40**: 79 (Nov.) 1919. Lusk, G. The Behavior of Various Intermediary Metabolites upon Heat Production, *ibid.* **49**: 453 (Dec.) 1921.

¹⁹ Hartmann,² p. 431.

²⁰ Hartmann,² p. 430.

DIABETIC COMA IN CHILDHOOD AND YOUTH

Can the treatment of severe diabetic acidosis which is used at present in the St. Louis Children's Hospital be recommended as a safe method for the youthful patient? The mortality among 16 patients so treated was 13 per cent,²¹ which was (a) six times the mortality among 54 children in diabetic coma whose plasma combining power was 15 volumes per cent or less and who were treated without alkali at the George F. Baker Clinic of the New England Deaconess Hospital between 1923 and December 1935, with 1 death, or a mortality rate of 1.8 per cent, (b) thirteen times the mortality for our 87 cases in which the onset of diabetes occurred when the child was less than 15 years old and the plasma carbon dioxide content was 15 volumes per cent or less (a severer test of therapy, for mortality increases with age), in which there was 1 death, or a mortality of 1 per cent, (c) twenty times the mortality for our 134 cases, if we adhere to our former classification of coma (fall of the plasma combining power to 20 volumes per cent or below), in which there was 1 death, or a mortality of 0.7 per cent.

It is unfortunate that in 2 of Dr. Hartmann's cases of pneumonia the diagnosis was not proved by roentgenographic or pathologic examination, because the frequent occurrence of fever, leukocytosis and râles during coma throws some doubt on such an unsubstantiated diagnosis. Of our 134 juvenile patients, 10 had râles and a total of 21 had infections, including acute infection of the respiratory tract, acute appendicitis, pyelitis, carbuncles and tuberculous pneumonia, all recovered, although the patient with tuberculosis died eight months later in a state sanatorium for tuberculous patients.

It is true that without alkali the average rise of the alkali reserve is slow—11 volumes per cent in Hartmann's series of 16 cases and 12 in ours eight hours after treatment. But if our comparable mortality rate is only 2 per cent and his with a more rapid rise is six times that, can we believe that the slow rise is harmful? Is it not more logical to believe that the rapid rise gives a false sense of security and that the fundamental fault in diabetes, namely, insulin insufficiency, has been overlooked?

Is the suggestion in Dr. Hartmann's paper substantiated—that diabetic coma because it occurs in Boston is of necessity of lesser degree than that which occurs in St. Louis? Do his chemical and clinical data

21 Hartmann,² p. 422, chart 4. Here he mentioned 16 cases, but on comparison with table 1, page 415, it appears that only 12 patients with severe acidosis were treated with the racemic lactate. Evidently he has added 4 cases from the 5 mentioned in the footnote on page 414 with a carbon dioxide content of 9.6, 11.5, 12.2, 21.7 and 26 volumes per cent, respectively, although it seems as though only the first 3 of these were relevant.

bear this out? Actually he has included in his series of 86 cases 14 in which the carbon dioxide content was over 35 volumes per cent—undeniably mild involvement. Even in the 19 cases in which the carbon dioxide content was between 25 and 35 volumes per cent the disorder was too mild to be considered in discussing the treatment of “severe acidosis,” although concomitant infection might have made the general clinical condition precarious.

The author is mistaken in the statement²² that he followed our methods of treatment, as his dosage of insulin was so much less than ours. The range in our series has been from 0.2 to 17 units per kilogram of body weight in twenty-four hours. Usually three fourths of the amount is administered in the first six hours by subcutaneous injection in small divided doses at intervals of from fifteen minutes to one hour. In 8 of our entire series of cases in which from 10 to 17 units per kilogram of body weight had been given, we are afraid that death would have intervened if only 2 units of insulin per kilogram of body weight had been given in the initial dose and none for six hours.

CONCLUSIONS

Three hundred and eighteen patients in diabetic coma with a carbon dioxide-combining power of the venous plasma of 20 volumes per cent or less have been treated without alkalis, with a mortality of 11.9 per cent. Among the last 42 cases there were 3 deaths, giving a mortality of 7.1 per cent. In 1 of these 3 fatal cases insulin was not given because of an error in diagnosis. The second patient died eight days after relief from acidosis was obtained, as a result of infection of the genito-urinary tract. The third patient died twenty days after relief from acidosis was obtained, as a result of infection of the leg. Considering children aged 15 years or less at the time of the coma, there has been only 1 death among 87 patients with an initial carbon dioxide-combining power of the plasma of 20 volumes per cent or less and 1 death (the same patient) among 54 with an initial carbon dioxide-combining power of 15 volumes per cent or less. Until data are reported which show better results than those obtained with our methods, often previously described, we see no reason to adopt more complicated procedures involving the use of alkalis or, specifically, sodium lactate which in the hands of their originators yield results inferior to ours.

No universal rule for the administration of insulin in coma is possible, because insulin must be given according to the severity of the coma, determined clinically and chemically, the age of the patient, the body weight, the duration of the diabetes as well as of the coma and the preceding treatment, particularly with insulin. Believing that one cannot

predict the course of diabetic coma for six hours in advance, we disapprove of an endeavor to give a single dose of insulin and no other until the end of that period

Our results have been secured by the use of (1) insulin given subcutaneously, and at times intravenously, every fifteen to thirty minutes in doses of 20 to 50 units (occasionally as high as 100 units, especially intravenously) amounting in the average case to approximately 200 units in twenty-four hours (2) the liberal use of salt solution subcutaneously and often intravenously as well to combat dehydration, (3) lavage of the stomach in nearly all instances unless the attending doctor accepts full responsibility for its omission, (4) liquids by mouth at an initial rate not to exceed 100 cc hourly and (5) unless 50 Gm of soluble carbohydrate or more is taken in the first twelve hours and again in the second twelve hours, dextrose intravenously or subcutaneously, and (6) always an endeavor to protect and stimulate the circulation by good nursing and by the use of epinephrine and ephedrine for falling blood pressure

STUDIES OF UROBILINOGEN

II UROBILINOGEN IN THE URINE AND FECES OF SUBJECTS WITHOUT EVIDENCE OF DISEASE OF THE LIVER OR BILIARY TRACT

CECIL JAMES WATSON, M D

MINNEAPOLIS

The tests for urobilinogen in the urine and feces which are commonly employed in the clinical study of jaundice and of hepatic function have not met with general approval, because of the varying and indefinite results obtained. In a recent review of the literature on tests of hepatic function by Soffer¹ this was in effect the conclusion reached. When one considers the varying dilution of the urine as well as the varying hourly excretion of the normal traces of urobilinogen in the urine (Bang²) and the much larger amounts present in the normal feces (Singer³), in which the concentration also is subject to wide variation, and when one considers further the daily and even hourly variations in the degree of urobilinuria in pathologic states, it is little wonder that qualitative tests, such as those of Ehrlich⁴ and Schlesinger,⁵ and roughly quantitative procedures, such as those of Wilbur and Addis⁶ and Wallace and Diamond,⁷ have often yielded confusing results. The need for knowledge of the per diem excretion of urobilinogen has been recognized by many, among whom von Muller⁸ and Gerhardt⁹ were

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1 Soffer, L. J. Present Day Status of Liver Function Tests, *Medicine* **14** 185, 1935

2 Bang, O. Klinische Urobilinstudien in Sonderheit an normalen und "lebergessunden" Personen. Die Wirkung kohlehydratknapper Kost auf die Urobilinausscheidung, die Urobilinurie der Diabetiker, *Acta med Scandinav*, supp 29, 1929, p 1

3 Singer, K. Studien zum Problem der Blutmauserung. Ueber den Einfluss der Ernährung auf die Urobilinalgusscheidung mit dem Fazes, *Wien Arch f inn Med* **20** 59, 1930

4 Ehrlich, P. Ueber die Dimethylamidobenzaldehydreaktion, *Deutsche med Wchnschr* **27** 151, 1901

5 Schlesinger, W. Zur klinische Nachweis des Urobilins, *Deutsche med Wchnschr* **29** 561, 1903

6 Wilbur, R. L., and Addis, T. Urobilin. Its Clinical Significance, *Arch Int Med* **13** 235 (Feb) 1914

7 Wallace, G. B., and Diamond, J. S. The Significance of Urobilinogen in the Urine as a Test for Liver Function, *Arch Int Med* **35** 689 (June) 1925

8 von Muller, F. Ueber Ikterus, *Jahresb d schles Gesellsch f vaterl Cult (Med Sekt)* **70** 1 1893

9 Gerhardt, D. Ueber Urobilin, *Ztschr f klin Med* **32** 303, 1897

the earliest Eppinger and Charnas¹⁰ and later Eppinger¹¹ made a considerable advance in the study of this subject. Employing more reliable methods, Lichtenstein and Terwen,¹² Adler and Bressel¹³ and I¹⁴ further demonstrated the potential value of estimation of urobilinogen. As yet, however, there has been no systematic investigation of the daily excretion of urobilinogen in the various types of jaundice and hepatic disease. By this is meant that the number of instances of any one disease has been too small in previous studies to permit of urobilinogen estimations in the study of this group of diseases.

In a separate communication¹⁵ reasons were given for distrusting the methods depending on the characteristics of urobilin, and an improved method for the quantitative estimation of urobilinogen was described. This method has been used in a study of the urobilinogen excretion of two hundred and five subjects. The present communication deals with the excretion of urobilinogen by normal subjects and by subjects suffering from various abnormal states, such as fever, malnutrition, inactivity, anemia and hematopoietic disease, in all of which jaundice or hepatic disease, if present, was not the primary or prominent pathologic process. This investigation is introductory and particularly intended to serve as a control for that reported in paper III of this series, which will follow. In paper III the excretion of urobilinogen in one hundred and thirty-five cases of the common forms of jaundice and hepatic disease will be discussed, and it will be shown that the various forms of jaundice are rather uniformly characterized by per diem excretion of urobilinogen of different magnitudes, which has evidently not been emphasized sufficiently in the past. This is particularly true for the distinction of obstructive jaundice due to neoplastic disease from other forms of jaundice. It has been found that a heightened excretion of urobilinogen in the urine, when studied with the method described, is an almost constant accompaniment of hepatic dysfunction or diffuse hepatic disease. In a later communication a com-

10 Eppinger, H, and Charnas, D. Was lehren uns quantitativen Urobilin Bestimmung im Stuhl? *Ztschr f klin Med* **78** 387, 1913

11 Eppinger, H. Die hepatolienalen Erkrankungen, Berlin, Julius Springer, 1920, pp 76-91

12 Lichtenstein, A, and Terwen, A. J. L. Ueber Blutmauserung und Urobilinausscheidung, *Deutsches Arch f klin Med* **149** 113, 1925

13 Adler, A, and Bressel, M. Urobilinogenbestimmung in Stuhl und Harn mittels der neuen Extraktionsmethode, *Deutsches Arch f klin Med* **155** 326, 1928

14 Watson, C. J. The Average Daily Elimination of Urobilinogen in Health and in Disease, with Special Reference to Pernicious Anemia, *Arch Int Med* **47** 698 (May) 1931

15 Watson, C. J. Concerning Urobilinogen. I. An Improved Method for the Approximate Quantitative Estimation of Urobilinogen in Urine and Feces, *Am J Clin Path* **6** 458, 1936

parative study of urobilinogen excretion, biomsulfalein retention and galactose tolerance in hepatic disease will be described. From this study it appears that, of the three tests, the determination of the daily amounts of urobilinogen in the urine and feces provides the most reliable information regarding the function of the liver and the causes of jaundice.

MATERIAL AND METHODS

The quantitative method employed in this investigation has been described in detail in paper I of this series¹⁵, the most important features of the method are given briefly in the following paragraphs.

1 Feces. A 10 Gm portion of the well mixed collection of feces for a four day period is thoroughly ground in a mortar with a few cubic centimeters of distilled water and diluted further to a total of 300 cc or only to 100 cc in case the feces are obviously acholic. This mixture is poured into a 500 cc Erlenmeyer flask containing 100 cc of a 20 per cent solution of ferrous sulfate (20 Gm of ferrous sulfate, 92 cc of water). Prior to solution the ferrous sulfate is powdered in a mortar. Finally, 100 cc of a 10 per cent solution of sodium hydroxide is added with constant mixing. The flask is corked and allowed to stand for one hour¹⁶. To 2 or 3 cc of the filtrate an equal amount of a modified Ehrlich's reagent¹⁷ is added, and then several cubic centimeters of a saturated aqueous solution of sodium acetate. Depending on the intensity of the color that develops, from 1 to 50 cc of the filtrate is used in the quantitative procedure. Thus, if the color is intense, 1 cc or even less will suffice, if pale red, from 5 to 10 cc, if faint, 25 cc, if absent, 50 cc. It is desirable that the amount of filtrate chosen should be only enough so that the final colored solution does not exceed 100 cc and that its color is not more than 50 per cent on the standard scale to be described. The amount of filtrate decided on is placed in a 125 cc pear-shaped separatory funnel, covered with 30 cc of purified petroleum benzine (petroleum ether)—after the filtrate is diluted to 20 cc with distilled water if less than this amount of filtrate was used—and then strongly acidified with glacial acetic acid and shaken vigorously for several seconds. After separation the aqueous fraction is extracted twice more with purified petroleum benzine. The combined solution of petroleum benzine is washed twice with water and then shaken vigorously with 1 or 2 cc of the modified Ehrlich reagent. At least twice as much of a saturated aqueous solution of sodium acetate is added, the maximum color now appearing. After vigorous shaking the colored solution is separated into a 100 cc graduated cylinder, and the petroleum benzine is again extracted with Ehrlich's reagent. This is repeated until the urobilinogen has been entirely removed (there is no further development of color). Each extraction is followed by the addition of sodium acetate, shaking and separation of the aqueous fraction into the cylinder. The colored solution is then made up to a volume convenient for calculation and mixed, and a sufficient amount is poured out to

16 Slightly lower values are obtained if the mixture is allowed to stand over night. For this reason the values given subsequently, as well as in part III, are undoubtedly slightly too low, since the mixture was allowed to stand over night in most of these instances.

17 This contains 0.7 Gm of paradimethylaminobenzaldehyde, 150 cc of concentrated hydrochloric acid and 100 cc of distilled water.

fill the right hand test tube of a Hellige-Dunning colorimeter¹⁸ Should the intensity of color be greater than 50 per cent of the standard, a further dilution is made, as comparisons are most accurate between 20 and 50 per cent

Calculation

$$\frac{\text{Cc of ferrous hydroxide mixture}}{\text{Gm of feces}} \times \frac{\text{Cc of final colored solution}}{\text{Cc of filtrate used}} \times \text{percentage of color standard} \times \frac{\text{weight of 4 day amount of feces}}{100} \times \frac{1}{\text{No of days' collection of feces}} = \text{Mg of urobilinogen per day}$$

Example

$$\frac{500}{10} \times \frac{45}{3} \times 0.35 \times 2.8 \times \frac{1}{4} = 183.7 \text{ mg per day}$$

Standardization of the colorimeter in terms of crystalline mesobilirubinogen (urobilinogen) has been described in the publication already referred to¹⁵

2 Urine A twenty-four-hour sample of urine is collected in a dark bottle containing approximately 5 Gm of sodium carbonate and 100 cc of purified petroleum benzine¹⁹ After collection the urine is separated from the petroleum benzine and measured Fifty cubic centimeters of the mixed urine is placed in an Erlenmeyer flask of 300 or 500 cc capacity To this is added, with thorough mixing, 25 cc of 20 per cent ferrous sulfate (5 Gm of the powdered crystals of ferrous sulfate dissolved in 25 cc of water) and 25 cc of 10 per cent sodium hydroxide After one hour a qualitative test on the filtrate determines the optimal amount for the quantitative procedure The amount chosen is treated in the same way as given previously for the feces The extraction of urobilinogen from the petroleum benzine is carried out in the manner given for the feces A comparison is then made in the colorimeter The calculation is as follows

$$\frac{100}{50} \times \frac{\text{Cc of final colored solution}}{\text{Cc of filtrate used}} \times \frac{\text{Percentage of standard}}{\text{Vol of 24 hour urine}} \times \frac{100}{100} = \text{Mg of urobilinogen in 24 hours}$$

Example (hepatic dysfunction)

$$\frac{2 \times 20 \times 0.18 \times 14}{2} = 50.4 \text{ mg in 24 hours}$$

18 A permanent glass standard colorimeter for determinations of phenol-sulphonphthalein in urine obtained from Hynson, Westcott and Dunning Co, Baltimore

19 In paper I results of comparative estimations following different methods of collecting the urine were given The majority of the results which are given here and in paper III were obtained after collection of the urine in ferrous hydroxide It was shown in paper I that the collection under petroleum benzine is somewhat more efficient, for this reason the values to be given here and in part III are slightly low

Data on the Urinary Excretion of Urobilinogen

Case	Diagnosis	Sex	Age	Hemo globin, %	Icterus Index	Urobilinogen Excretion, Mg per Day	
						Urine	Feces
Group 1	Normal Subjects and Hospital Patients Without Fever, Anemia, Jaundice or Other Evidence of Disease of the Liver or Biliary Tract						
A Feces and Urine							
1	Normal	M	25	85		Trace	156.4 189.0
2	Normal	M	29	89		0.93	108.0
3	Normal	M	24	102		2.16	279.4
4	Normal	F	22	85		0.46	40.9
5	Normal	M	55	90		2 mo later	42.0
6	Normal	F	21	85		Trace	162.0
7	Normal	M	40	98		Trace	180.2
8	Normal	M	34	90		Negative	261.2
9	Normal	M	23	85		0.40	278.4
10	Normal	M	19	96		3.60	199.8
11	Normal	M	24			Trace	140.4
12	Normal	M	25	87		1.70	259.9
13	Normal	M	26	101		3.40	89.8
14	Normal	M	24			0.35	158.3
15	Normal	F	22	82			189.0
16	Epilepsy	M	33	101		0.80	76.0
17	Spinal cord tumor (no paralysis)	M	52	97		0.50	262.5
						0.70	201.2
B Additional Determinations							
18	Normal	F	22			0.98	
19	Normal	F	20			1.20	
20	Normal	F	22			1.70	
21	Normal	M	25			2.00	
22	Fracture of femur	M	40			1.10	
23	Quiescent tuberculosis of spine	F	42			Trace	
24	Obesity (397 pounds)	M	46			0.70	
25	Injury to eye	M	46			1.80	
26	Gastric ulcer	M	32			Trace	
Group 2 Persons with Mild Infection, Inanition or Inactivity (No Jaundice or Anemia)							
27	Atrophy of optic nerve, sciatic neuritis	M	37	91		Trace	54.2
28	Chronic arthritis	M	31	81		1.00	93.8
29	Multiple neuritis	F	38	99		0.24	22.8
30	Inanition following burns, pyelonephritis, nephrolithiasis	F	17	82		Negative	38.6 25.1
31	Large carcinoid tumor of cecum, extreme inanition	F	63	77			8.8
Group 3 Persons with Conditions Associated with Fever							
32	Subacute bacterial endocarditis, constant fever, 100 to 103 F	M	45	63	14	Trace	
33	Subacute bacterial endocarditis, continuous fever, 101 to 103 F, 26,000 leukocytes	M	17	52	28	0.85	
34	Undulant fever, temperature 99 to 101 F, no jaundice	F	24	74		0.80	
35	Infectious arthritis, fever, 99 to 102 F, no jaundice	F	42	57		Negative	
36	Hodgkin's disease with fever, anemia, splenomegaly	M	34	36			225.8
37	Hodgkin's disease, intermittent fever splenomegaly, anemia	M	35				
	Febrile			51	18	35.3	269.8
	Afebrile			50	12		127.4
38	Malaria (therapeutic)	M	31	76	10	10.9	233.9
39	Pneumonia following postoperative atelectasis, mild icterus	M	38	89	26	37.6	
40	Pelvic cellulitis and bacteremia, jaundice	F	38	70	27	20.5	208.2
41	Pulmonary abscess, empyema, no jaundice	M	37	55		8.3	
42	Lobar pneumonia, slight icterus	F	22	86	20	32.5	325.5

Data on the Urinary Excretion of Urobilinogen—Continued

Case	Diagnosis	Sex	Age	Hemo- globin, %	Icterus Index	Urobilinogen Excretion, Mg per Day	
						Urine	Feces
Group 1 Persons with Anemia or Other Hematopoietic Disease							
43	Pernicious anemia	F	44				
	Prior to liver therapy			20	27	6.70	587.0
	After liver therapy			44	11	0.30	210.0
44	Pernicious anemia	F	40				
	Prior to liver therapy			28	22	0.70	600.0
	After liver therapy			65			189.3
45	Pernicious anemia	M	52				
	Prior to liver therapy			15	11	16.10	338.0
	After liver therapy			53		0.20	61.0
46	Pernicious anemia, prior to liver therapy	M	25	44		2.90	622.5
47	"Pernicious" type of anemia with pregnancy, free hydrochloric acid in gastric contents			24	16	1.90	330.2
48	Hyperchromic anemia with myxedema, 2,480,000 erythrocytes	F	51	65	10	Trace	22.5 46.3 66.1 25.2 126.7
				49 67			
49	Hyperchromic anemia with lymphatic leukemia, leukopenia with many immature lymphocytes, no enlargement of spleen, liver or lymph nodes	F	38	60			27.0
50	Hypochromic anemia due to bleeding hemor- rhoids	F	39	51	13	0	71.9
51	Idiopathic hypochromic anemia, dysphagia, koilonychia, hypochlorhydria	F	43	54 56		Trace	53.8 53.3
52	Idiopathic hypochromic anemia, achlorhydria	F	47	40	6	0	45.4
53	Idiopathic hypochromic anemia, menorrhagia, glossitis, dysphagia, marked koilonychia, free hydrochloric acid	F	40	44		Trace	21.0
54	Idiopathic steatorrhea (nontropical sprue), Hypochromic anemia	M	42	66	4.5	4.50	127.5
55	Hypochromic anemia of pregnancy	F	19	44	5.0	Trace	107.0
56	Severe anemia following pregnancy, no response to liver therapy, improvement following trans- fusions	F	29	13	10.0		24.0
57	Skin tuberculosis, Little's disease, mild hypo- chromic anemia	M	18	76		0.40	34.4
58	Mild hypochromic anemia	F	18	74		Trace	41.6
59	Osteomyelitis, hypochromic anemia, low grade fever	F	54	60		Negative	16.5
60	Probable Banti's disease, 8 months' pregnancy, hypochromic anemia	F	24	53	6	20.70	121.9
	16 months later, spleen remains markedly enlarged			78		1.60	210.6
61	Hypochromic anemia with multiple bone metas- tases from carcinoma of breast	F	43	25	6		56.0
62	Myelophthisic anemia with aleukemic lymph adenosis	M	53	34	9	1.40	6.5
63	Lead poisoning, colic, basophilic stippling	M	50	60			173.4
64	Polycythaemia vera, large subcutaneous hema- toma in flank and loin appeared several days before admission, 7,400,000 erythrocytes	M	61	129	11	2.10 9.80	491.0 431.7
	Two months after disappearance of hematoma			114	14	3.30	191.6
65	Polycythaemia vera, 7,800,000 erythrocytes	M	60	106			104.1
66	Polycythaemia vera (3 years), angina pectoris, recent congestive heart failure, 5,850,000 eryth- rocytes	M	53	122		1.70	344.7
67	Polycythaemia vera, 7,750,000 erythrocytes	M	53	134	27 26	Trace	110.6
68	Polycythaemia vera, 6,700,000 erythrocytes	F	57	118	17	Trace	347.6
69	Polycythaemia vera, 5,950,000 erythrocytes	M	69	124	7	Negative	37.5

Throughout this investigation, as well as that which is reported in paper III, specimens of urine giving a negative or low value with the quantitative method were subjected to the ordinary qualitative tests of Ehrlich and Schlesinger. In a few instances only, one or the other or both of these tests were found to be weakly or questionably positive. However, a weak Ehrlich reaction is not necessarily indicative of the presence of urobilinogen. In certain instances it was found that the petroleum benzine extract of urine which exhibited a weak Ehrlich reaction did not show the characteristics of urobilin, i. e., absorption at 495 millimicrons and green fluorescence with zinc after prolonged exposure to light, nor did these characteristics appear after application of the Garrod-Hopkins²⁰ precipitation with ammonium sulfate followed by exposure to light. On one occasion the Ehrlich reacting substance, after acidification of the filtrate, was not extracted by petroleum benzine, and in this instance the absorption spectrum of the urine with Ehrlich's reagent was not that of the urobilinogen-aldehyde compound. The maximum absorption of the former was found to be at 574.6 millimicrons, and weaker absorption was noted at 534.7 millimicrons, while a urobilinogen-aldehyde solution exhibited absorption at a maximum of 561.1 millimicrons. On superimposition of these spectra, a wide separation of the bands was observed. This substance could not be identified, but it did not appear to be indole or skatole, since it was not extracted with petroleum benzine and since the Ehrlich reaction did not disappear after the addition of sodium acetate.²¹

The studies composing paper I include estimations of the excretion of urobilinogen in sixty-nine instances. These have been divided into four groups as follows:

	No. of Subjects
Group 1 Normal subjects and hospital patients not having fever, anemia, jaundice or any evidence of disease of the liver or of the biliary tract	
A For whom both urine and feces were investigated	17
B For whom only urine was investigated	9
Group 2 Subjects in whom mild infection, inanition or inactivity was the only abnormal factor present	5
Group 3 Hospital patients having various febrile diseases	11
Group 4 Patients with anemia, leukemia, polycythemia or some other hematopoietic disease	27

The percentage of hemoglobin was estimated by the Sahli method, 17 Gm of hemoglobin per hundred cubic centimeters corresponding to 100 per cent. The icterus index was determined by Bernheim's²² modification of Meulengracht's method.

20 Garrod, A. E., and Hopkins, F. G. On Urobilin. I. The Unity of Urobilin, *J. Physiol.* **20** 112, 1896.

21 Terwen, A. J. L. Ueber eine neues Verfahren zur quantitativen Urobilinbestimmung im Harn und Stuhl, *Deutsches Arch. f. klin. Med.* **149** 72, 1925.

22 Bernheim, A. R. The Icterus Index (a Quantitative Estimation of Bilirubinemia). An Aid in Diagnosis and Prognosis, *J. A. M. A.* **82** 291 (Jan. 26) 1924.

COMMENT ON OBSERVATIONS

The results noted in the accompanying table indicate that the urinary urobilinogen, as determined by the method described, varies normally between 0 and 4 mg per day, usually from 0.5 to 2 mg. In the earlier investigation already referred to¹⁴ the urobilinogen content of the feces in thirteen normal subjects varied between 54 and 245 mg per day. The values noted in the present investigation indicate a range from 40 to 280 mg, so it is evident that there is rather wide variation in the normal excretion of urobilinogen in the feces. Inactivity, inanition or low grade infection or a combination of these appears to be accompanied with a decrease in the amount excreted.

The values in group 3 demonstrate that fever alone is insufficient to cause increased excretion of urobilinogen in the urine. Weiss²³ has emphasized this fact by stating that urobilinuria and fever are not coordinated phenomena. The type of infection appears to be a more important factor. Urobilinuria in pneumonia has been emphasized by Weiss,²³ Adler and Biessel¹³ and Simpson,²⁴ and the latter author was one of the first to stress its occurrence in malaria. Weiss²³ stated that febrile conditions are often associated with an increased excretion of urobilin in the feces. The present results appear to bear out this statement, although in only two instances were the amounts sufficiently high to be decisive. The first (case 42) was an instance of lobar pneumonia with icterus, and the second (case 37), one of Hodgkin's disease during a febrile period. In neither could the icterus be said to have been more than partly hemolytic in origin, since the large amount of urobilinogen in the urine pointed to a considerable reduction in the hepatic function. It is worthy of note that in the instance of Hodgkin's disease mentioned the output of urobilinogen was more than halved after the fever abated. The possible relationship of fever, anemia and an increased destruction of blood in Hodgkin's disease, as measured by the excretion of urobilinogen, is deserving of further study. An instance of profound hemolytic anemia in a patient with Hodgkin's disease and persistent fever has recently been observed, the findings will be presented in paper III of this investigation in the section devoted to hemolytic jaundice.

Unfortunately, it is difficult, and at times impossible, to obtain satisfactory collections of stools from persons suffering from severe febrile disease. In several of the cases in group 3 attempts were made to obtain four day collections of feces, but the amounts were so small that no

23 Weiss, M. Ueber Urobilin und seine diagnostische Verwertung, Wien Arch f inn Med **20** 39, 1930.

24 Simpson, G. C. E. On the Quantitative Estimation of Urobilin in the Excreta, and Its Value as a Measure of Haemoglobin Metabolism, Biochem J **6** 378, 1911.

reliance could have been placed on determinations based on them. Since in normal subjects a four day collection of feces weighs between 300 and 500 Gm, estimations based on collections weighing less than 250 Gm must be expected to yield relatively lower values. Assuming that none of the feces for the period are lost, this is probably because of an increased resorption of urobilinogen incident to constipation (Wilbur and Addis⁶)

The results in the cases of pernicious anemia are entirely comparable with those which I have previously reported¹⁴. The marked drop in the amount of urinary urobilinogen coincident with the reticulocyte response to liver therapy was again noted, as was also the considerable decrease in the amount of urobilinogen in the feces. It is noteworthy that in two instances (cases 44 and 46) a considerable increase of urobilinogen was observed in the feces without an increase in the urine. The question of the relationship of urobilinuria to an increased destruction of blood and simple "overflow" of urobilinogen into the general circulation will be discussed in paper III of this series. With the exception of one patient who had a pernicious type of anemia with pregnancy, the other cases of anemia investigated were characterized by normal or less than normal amounts of urobilinogen in the feces. The findings in cases 48 and 49 are particularly significant, since they indicate that hyperchromic anemia need not be accompanied with an increased urobilinogen excretion. Two patients with leukemia, not included among those just mentioned, are of interest in this connection. Both of these patients exhibited a pernicious type of anemia with slight icterus, for one (aleukemic lymphadenosis was proved at necropsy) the amount of urobilinogen excreted in the feces was 350 mg per day, while the second patient, who had lymphatic leukemia, excreted 1,005 mg per day during the period studied. This supports the belief that leukemia may be accompanied with an increased destruction of blood. As a result of histologic studies Jaffe²⁵ stated that he believed that this is the most important factor in the development of leukemic anemia.

In three of the six instances of polycythaemia vera a definite although only moderate increase of the urobilinogen content of the stools was noted (cases 64, 66 and 68). In the first of these, however, the local formation of bilirubin in a large hematoma may have been responsible for the increased amount of urobilinogen in the feces. Some months after the disappearance of the hematoma, the excretion of urobilinogen in the feces had returned to a normal level. Eppinger¹⁰ gave values for four patients with polycythaemia vera, in two of these the output of urobilinogen in the feces was slightly increased and in the other two normal.

25 Jaffe, R. H. Erythropoiesis, *Folia haemat* 49 51, 1933

CONCLUSIONS

The amount of urobilinogen excreted in the urine in twenty-four hours by the normal adult varies between 0 and 4 mg, usually being from 0.5 to 2 mg. The normal range for the feces is between 40 and 280 mg per day, usually from 100 to 250 mg.

Inanition, inactivity or a low grade infection tends to lower the excretion of urobilinogen in the feces, fever of any considerable degree probably tends to increase the amount. Fever alone does not cause an increase in the excretion of urobilinogen in the urine, this is evidently dependent on the type and severity of the infection.

In addition to the various forms of hemolytic jaundice, which will be discussed subsequently, increases of the excretion of urobilinogen were again noted in the feces in cases of pernicious anemia and in instances of Hodgkin's disease and of leukemia. Low values were encountered in certain cases of secondary hyperchromic anemia and in all the cases of hypochromic anemia investigated. Slight increases were observed in half the cases of polycythaemia vera.

STUDIES OF UROBILINOGEN

III THE PER DIEM EXCRETION OF UROBILINOGEN IN THE COMMON FORMS OF JAUNDICE AND DISEASE OF THE LIVER

CECIL JAMES WATSON, M D

MINNEAPOLIS

In earlier communications¹ reference was made to the necessity of determining the daily amounts of urobilinogen in the feces and urine rather than attempting to interpret results obtained with qualitative tests. A method for the approximate quantitative estimation of the urobilinogen content was described, and in part II of this series of papers results were given which may be used as controls for the series to be presented here. The former group included normal persons, patients with mild infection, inanition, fever of various cause and anemia and hematopoietic disease of various types. The present investigation deals with the excretion of urobilinogen in the common forms of jaundice and hepatic disease.

MATERIALS AND METHODS

One hundred and thirty-five patients² with jaundice or hepatic disease were studied with regard to the per diem excretion of urobilinogen. Their cases may be divided conveniently into seven groups, as follows:

	No of Cases
1 Cholecystitis and cholelithiasis	
A With obstructive jaundice of variable degree but without complications such as severe infection, anemia or cirrhosis secondary to long-standing biliary obstruction (in the majority of these cases clinical or operative evidence of a stone in the common duct was obtained)	21
B With complications of the foregoing type	20

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1 Watson, C J (a) The Average Daily Elimination of Urobilinogen in Health and in Disease, with Special Reference to Pernicious Anemia, *Arch Int Med* 47 698 (May) 1931, (b) Studies of Urobilinogen I An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, *Am J Clin Path* 6 458, 1936, (c) Studies of Urobilinogen II Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, *Arch Int Med*, this issue, p 196

2 Several of these patients were observed in the medical service at the Minneapolis General Hospital. Permission to study these patients was given by Dr George E Fahr and Dr Nathaniel H Lufkin.

2 Obstructive jaundice due to neoplastic disease of the biliary tract	18
3 Diffuse hepatic disease	
A Cirrhosis of the liver with considerable jaundice	10
B Cirrhosis of the liver with jaundice and evidence of increased destruction of blood	7
C Cirrhosis of the liver with slight or no jaundice	8
D Acute catarrhal jaundice	11
4 Congestive heart failure with jaundice, enlargement of the liver or ascites	11
5 Carcinoma of the liver or peritoneum with or without ascites and without jaundice	10
6 Miscellaneous hepatic diseases of secondary nature	6
7 Hemolytic jaundice	
A Familial or congenital	10
B Acquired	3

The twenty-four hour amount of urobilinogen in the urine was estimated according to the improved method described previously³. The per diem excretion of urobilinogen in the feces over a four day period was determined by the same method in the majority of instances, particularly if there was any question as to the degree of biliary obstruction or the rate of destruction of the blood. It was at times impossible to obtain satisfactory collections of feces from very sick patients, especially those with marked congestive heart failure or severe febrile disease. In a few instances only qualitative tests for urobilin and urobilinogen were carried out. For this purpose 1 or 2 Gm of feces was ground with 5 or 10 cc of a saturated alcoholic solution of zinc acetate. The filtrate was examined for green fluorescence in front of a point lamp and was then tested for urobilinogen by the addition of 2 or 3 cc of the modified Ehrlich reagent^{1b} followed by 3 or 4 cc of a saturated solution of sodium acetate. Depending on whether weak, moderate or strong, the intensity of these qualitative reactions is recorded as +, ++ or +++.

The icterus index was determined according to Meulengracht's method (Bernheim's modification⁴). Blood for this determination was obtained while the patient was fasting. The qualitative van den Bergh reaction was carried out in duplicate, with fifteen minutes between the two reactions. The developing color of the second reaction was compared with the fully developed color of the first, the approximate percentage appearing within and after the first minute being noted. Reactions were recorded as follows: (1) direct prompt (all the color developing within one minute), (2) biphasic prompt (more than 50 per cent of the color developing within one minute), (3) biphasic delayed (more than 50 per cent of the color developing after one minute) and (4) delayed (all the color developing after one minute). If none of these appeared, the serum was examined for an indirect reaction after treatment with alcohol in the usual manner.

The percentage of hemoglobin was determined by the Sahli method. Seventeen grams of hemoglobin per hundred cubic centimeters was equivalent to 100 per cent with the apparatus used.

3 Watson^{1a, b}

4 Bernheim, A. R. The Icterus Index (a Quantitative Estimation of Bilirubinemia). An Aid in Diagnosis and Prognosis, J. A. M. A. **82** 291 (Jan 26) 1924.

TABLE 1—Data on the Excretion of Urobilinogen

Group 1 Cholecystitis and Cholelithiasis

Case	Condition	Sex	Age	Operation or Autopsy	Icterus Index	Van den Bergh Reaction	Urobilinogen Excretion, Mg per Day	
							Urine	Feces
1	Gallstone colic, receding jaundice	M	72	Operation	16	Biphasic delayed	0.90	+++
2	Gallstone colic, recent slight jaundice	F	44	Operation	16	Biphasic delayed	2.10	125.00
3	Gallstone colic, jaundice, 1 week	M	53	Operation	20	Biphasic delayed	4.90	317.20
4	Gallstone colic, jaundice, 3 weeks	F	22	Operation	64	Biphasic delayed	2.20	++
5	Previous cholecystectomy, stone in common duct	F	44	Operation	21	Biphasic delayed	0.30	
6	Repeated colic, mild jaundice	F	53	Operation	15	Delayed	0.20	
7	Painless jaundice, 1 week	F	65	Operation			Trace	50.00
8	Eight days later, jaundice now of 2 weeks' duration						0	10.60
9	Repeated colic, recent jaundice	M	60		32		1.60	+++
10	Repeated colic, intermittent jaundice	F	56		29	Biphasic prompt	0.80	
11	Repeated colic, intermittent jaundice	F	43	Operation	96		4.00	148.00
12	Repeated colic, jaundice, 1 month	F	32	Operation	41	Biphasic delayed	3.50	83.20
13	Previous cholecystectomy, stricture of common duct	M	30	Operation	14		0	
14	Repeated colic, intermittent jaundice	F	49	Operation	85	Biphasic delayed	Trace	1 1
15	Repeated colic, slight jaundice	M	59	Operation	21		Trace	
16	Repeated colic, intermittent jaundice	F	63	Operation	12		0	
17	Repeated colic, previous jaundice	F	71	Operation	30	Delayed	2.20	
18	Slight icterus, pain in right upper quadrant of abdomen	M			18		3.50	
19	Colic in right upper quadrant of abdomen, jaundice, two weeks	F	26		66	Biphasic delayed	6.20	37.10
20	Repeated colic, intermittent jaundice	F	40	Operation	26	Biphasic delayed	2.10	225.00
21	Repeated colic, recent jaundice	F	58	Operation	30	Biphasic	0	67.50
	Repeated colic, previous jaundice	F	74		17	Biphasic	2.80	25.40
B With Obstructive Jaundice and with Different Complications, Such as Severe Infection, Particularly of the Biliary Tract, or Cirrhosis Secondary to Long Standing Biliary Obstruction								
22	Acute cholecystitis, cholangitis, common duct stone	F	49	Operation	60		10.90	170.20
23	Subphrenic hematoma and abscess following cholecystectomy, sandlike concretions in hepatic duct, severe anemia	F	32	Autopsy	33	Biphasic delayed	37.90	
24	Long standing recurrent cholangitis with common duct stone, daily temperature, 104 or 105 F, chills, increasing jaundice, acute and chronic inflammation in portal spaces of liver with biliary cirrhosis	F	51	Autopsy	52	Biphasic delayed	53.50	246.80
25	Acute cholecystitis	F	63	Operation	19		6.90	
26	Continuous jaundice for 2 years following cholecystectomy, large liver, common duct stricture, biliary cirrhosis	F	44	Autopsy	65		3.90	6.70
27	Acute cholecystitis	F	58		16	Delayed	8.00	
28	Continuous jaundice for 6 months, large liver, finely nodular at operation (biliary cirrhosis), large impacted stone removed from common duct, recovery	F	64	Operation	64	Biphasic prompt	26.20	10.00

29 Frequently recurring jaundice for 2 years, pain in right upper quadrant of abdomen, roentgen evidence of duodenal ulcer or adhesions, large liver, ascites, spontaneous improvement with disappearance of ascites and jaundice

30 Acute cholecystitis, during attack

31 Several days after subsidence of acute symptoms

32 Frequent gallstone colic with jaundice for 21 years, continuous jaundice for last 12 years, very large liver, finely roughened at operation (biliary cirrhosis)

33 Previous gallstone colic and empyema of gallbladder, deep jaundice for 6 weeks, recovery

34 Previous gallstone colic with frequent jaundice, present jaundice of 6 weeks' duration, large liver, finely granular at operation, recovery

35 Previous attacks of pain in right upper quadrant of abdomen for past 4 years, present attack of 2 weeks' duration with slight jaundice, low grade fever, leukocytes 16,700 evidence of heart failure, dyspnea on exertion, edema of ankles, large, tender liver, right hydrothorax

36 After 24 hour interval

37 Repeated attacks of colic in right upper quadrant for past year, marked jaundice, frequent pain of 3 weeks' duration, fever and leukocytosis, enlargement of liver

38 Four days later jaundice disappearing, no pain or tenderness remaining

39 Painless jaundice of 3 months' duration, large stones removed from common duct at operation, early biliary cirrhosis noted

40 Previous colic in right upper quadrant of abdomen, with jaundice, chills and fever (105° F) with present attack, deep jaundice

41 Marked improvement

42 Operation stone in dilated common duct

43 Repeated gallstone colic, present attack with jaundice, fever, pain and tenderness in right upper quadrant of abdomen, leukocytosis

44 Jaundice diminished, pain and fever gone, gallstone recovered from this 4 day collection

45 Removal of gallbladder and stones 4 years before, recurrent pain and jaundice 1 year before, short duration, present attack of jaundice and mild pain of 5 weeks' duration, no fever or leukocytosis, liver enlarged and firm

46 After interval of 2 weeks

47 Stone removed from common duct, liver finely granular

48 Recurrent icterus, chills and fever, loss of weight, operation

49 10 stones in common duct, autopsy large stone impacted just above ampulla, biliary cirrhosis

50 Acute cholecystitis, febrile stage, leukocytosis, pain, tenderness and rigidity in right upper quadrant of abdomen

51 After interval of 5 days, with subsidence of acute symptoms and findings, multiple stones present in common duct at operation

M	59	Operation	32	Biphasic prompt	13 50
I	25		9		20 80
					0 18
M	49	Operation	48	Biphasic prompt	25 60
I	27	Operation	208	Biphasic prompt	10 80
I	50	Operation	18	Biphasic prompt	17 70
					116 00
F	66		71	Biphasic	102 30
					53 00
F	58	Operation	71	Biphasic prompt	23 40
			29		2 30
F		Operation	79	Biphasic delayed	8 30
F	37	Operation	92	Prompt	4 20
			78		621 60
			19		165 00
			21		100 20
M	55	Operation	29	Delayed	15 20
					Trace
					174 40
M	35	Operation	48	Biphasic delayed	36 10
			20		8 90
F	63	Autopsy	22	Biphasic	7 50
F	43	Operation	34	Biphasic prompt	112 30
					10 70
					2 10

TABLE 1—Data on the Excretion of Urobilinogen—Continued

Group 2 Obstructive Jaundice Due to Neoplastic Disease in Biliary Tract									
Case	Condition	Sex	Age	Operation or Autopsy	Hemo- globin, %	Icterus Index	Van den Bergh Reaction	Urobilinogen Excretion, Mg per Day	
								Urine	Feces
42	Repeated gallstone colic for past 11 years, multiple small nonantony metastases (biopsy) in liver and adjacent to hepatic ducts, primary cause not determined, cholelithiasis	F	45	Operation	74	61	Biphasic prompt	Trace	1 60
43	Carcinoma of gallbladder with involvement of bile ducts and head of pancreas	M	72	Autopsy	71	150	Biphasic	0 04	0 13
44	Melanoma metastases in common duct, none in liver paren- chyma, large liver and finely granular surface	M	59	Autopsy	82	188	Biphasic prompt	1 60	17 90
45	Probable carcinoma of head of pancreas, definite evidence of hepatic metastases by thorium dioxide	M	68		66	160		Trace	0 70
46	Carcinomatosis of omentum, mesentery and retroperitoneal lymph nodes involving common bile duct, site of primary tumor not determined, no metastases in liver	M	75	Autopsy	91	192	Biphasic prompt	Trace	Trace
47	Carcinoma of head of pancreas	M	67	Operation	72	119	Biphasic prompt	0	4 70
48	Large retroperitoneal mass in region of head of pancreas, probably sarcoma (biopsy)	M	46	Operation	82	59		Trace	1 90
49	Carcinoma, probably primary in pancreas, multiple hepatic metastases shown with thorium dioxide	M	49		80	192	Biphasic	0	3 00
50	Carcinoma of head of pancreas	M	60	Autopsy	84	125	Biphasic prompt	Trace	0 57
51	Carcinoma of head of pancreas	M	63	Operation	77	127	Biphasic prompt	0	Trace
52	Previous gallstone colic, tumor filling common and hepatic ducts, microscopically adenocarcinoma, multiple stones in gallbladder	F	58	Operation	82	166	Biphasic	0	0 50
53	Painless jaundice of 6 months' duration, enlarged liver, ascites, operation revealed carcinoma involving ampulla of Vater and common hepatic bile ducts, biliary cirrhosis	F	46	Operation	76	122	Biphasic prompt	0	Trace
54	Jaundice, roentgen evidence of large gastric carcinoma, large nodular liver, blood in feces	M	59		40	61	Biphasic	0 30	4 80
55	Carcinoma of head of pancreas (biopsy)	M	62	Operation	73	67	Biphasic prompt	0	Trace
56	Deep jaundice, carcinomatosis proved by biopsy of cervical lymph node, death, autopsy denied	M	54		73	166	Biphasic	0	0
57	Jaundice for 3 months, carcinoma of gallbladder with metastases to liver	F	48	Autopsy	48	172	Biphasic prompt	0	1 50
58	Jaundice for 6 weeks, colic in right upper quadrant of abdo- men, marked fever, operation stones and purulent exu- date in gallbladder diffuse, hard infiltration of common duct, microscopically carcinoma	F	64	Operation	71	125	Biphasic	0	Trace
59	Jaundice for 2 weeks, epigastric pain, large, hard, nodular liver, widening of duodenal loop shown in roentgenogram, glycosuria, occult blood in feces, death, necropsy denied	F	64		79	61	Biphasic	0	0 90
Group 3 Diffuse Hepatic Disease									
A Cirrhosis of Liver with Considerable Jaundice									
60	Ascites edema, hypertensive congestive heart failure, ad- vanced cirrhosis of Laennec type	F	56	Autopsy	62	40	Biphasic	18 70	75 00
61	Cirrhophen cirrhosis, jaundice for 5 weeks, increasing ascites 8½ days later	F	53		80	74	Biphasic delayed	8 10	211 50

Case No.	Sex	Age	History	Physical	Laboratory	Pathology	Treatment	Outcome	Remarks
62	M	52	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	88	140	380 2740
63	F	12	Attack of painless jaundice 6 years, liver moderately enlarged, firm, spleen considerably enlarged	Jaundice for 6 weeks, splenomegaly, small liver (roentgenogram), melena, previous painless jaundice	Intermittent jaundice for 6 years, liver moderately enlarged, firm, spleen considerably enlarged	Autopsy	50	71	170
64	M	44	Attack of jaundice since infancy, jaundice for 8 months, tonsillitis, sinusitis, fatal septicaemia, no ascites, moderate anemia, advanced cirrhosis of Laennec type	Painless jaundice for 2 months, marked ascites	Painless jaundice for 2 years, marked ascites for 9 months, small liver (thorium dioxide), palpable spleen	Autopsy	82	60	1860
65	F	13	Attack of jaundice since infancy, jaundice for 8 months, tonsillitis, sinusitis, fatal septicaemia, no ascites, moderate anemia, advanced cirrhosis of Laennec type	Painless jaundice for 2 months, marked ascites	Painless jaundice for 2 years, marked ascites for 9 months, small liver (thorium dioxide), palpable spleen	Autopsy	59	76	Trace
66	F	29	Attack of jaundice since infancy, jaundice for 8 months, tonsillitis, sinusitis, fatal septicaemia, no ascites, moderate anemia, advanced cirrhosis of Laennec type	Painless jaundice for 2 months, marked ascites	Painless jaundice for 2 years, marked ascites for 9 months, small liver (thorium dioxide), palpable spleen	Autopsy	90	77	3240
67	M	69	Attack of jaundice since infancy, jaundice for 8 months, tonsillitis, sinusitis, fatal septicaemia, no ascites, moderate anemia, advanced cirrhosis of Laennec type	Painless jaundice for 2 months, marked ascites	Painless jaundice for 2 years, marked ascites for 9 months, small liver (thorium dioxide), palpable spleen	Autopsy	61	50	170
68	M	18	Attack of jaundice since infancy, jaundice for 8 months, tonsillitis, sinusitis, fatal septicaemia, no ascites, moderate anemia, advanced cirrhosis of Laennec type	Painless jaundice for 2 months, marked ascites	Painless jaundice for 2 years, marked ascites for 9 months, small liver (thorium dioxide), palpable spleen	Autopsy	63	69	090 440 150
69	F	46	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	72	136	4900
70	M	52	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	87	40	060
71	F	31	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	85	36	77700
72	M	44	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	85	36	31820
73	F	46	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	85	36	2070 3030 3110 3890
74	M	52	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	85	36	30700 13690
75	F	31	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	85	36	2460
76	M	69	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	85	36	6580
77	F	46	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	85	36	80330 1,25700 46120
78	M	52	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	85	36	22420
79	F	31	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	85	36	99000 89400
80	M	69	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	85	36	21100
81	F	46	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	85	36	43 35
82	M	52	Attack of painless jaundice 5 months previously, recurrence of 2 weeks' duration, enlarged spleen and liver, moderate ascites	Mild intermittent jaundice for 3 or 4 years, ascites, splenomegaly, hemoglobin 58% erythrocytes 2,830,000	Jaundice for 6 weeks, rapidly recurring icterus, coma and terminal hemorrhage from bowel, alcoholism, autopsy advanced cirrhosis with numerous adenomas	Autopsy	85	36	14620 2360

TABLE 1—Data on the Excretion of Urobilinogen—Continued

Case	Condition	Sex	Age	Date	Hemo- globin, %	Icterus Index	Van den Bergh Reaction	Urobilinogen Excretion Mg per Day	
								Urine	Feces
71	Marked improvement, reticulocytes 2%			11/27/34	80			35 50 3 80 2 90	63 40
	Spleen and liver remain enlarged and firm			1/12/35	77	14			
	Spleen and liver smaller			3/ 2/35					
	Spleen and liver are still easily palpable, no jaundice, patient feels well			4/23/35	83	11		0 20	186 60
				9/25/35					
72	Mild jaundice for 3 months, occasional vague distress in right upper quadrant of abdomen, abdominal distention, questionable ascites, small liver, enlarged spleen (thorium dioxide), erythrocytes 3,310,000	M	55	8/ 9/34	70	51	Biphasic prompt	251 40 56 20 85 50	56 20
				8/14					
				8/15		74		72 70 59 50	
				8/20					
				1/18/35					603 90
				1/23					470 00
				4/13/35					319 70
73	Chronic alcoholism, jaundice, ascites, enlarged liver, spleen not palpable, erythrocytes 4,100,000	M	52		81	91	Biphasic	108 10	
74	Icterus for 2 weeks, never previously, marked hepatic and moderate splenic enlargement, bilirubin in urine at height of jaundice, reticulocytes 12%, repeated blood transfusions	F	63	9/ 7/33	32	80		49 20	
				9/ 9					
				9/11	38	16	Indirect	12 70	755 00
				9/26					
				9/29	68	20			
				12/ 2	70				
				2/ 7/34					
75	Moderate ascites, no opportunity afforded for further urobilinogen studies	F	30	3/ 5		17	Indirect	29 50	500 20
	Splenomegaly, marked enlargement of liver, slight ascites, anemia for 2 years, reticulocytes 7%			3/16	47				1,107 00
	Erythrocytes 1,770,000			4/12				56 10	332 40
				5/11					952 00
				5/16				19 20	
				5/18	62	56		27 40	526 50
76	Chronic alcoholism, recurrent jaundice for 3 years, liver palpable, spleen markedly enlarged, mild edema of ankles, erythrocytes 2,900,000	M	45						

No.	Clinical History	Differential Diagnosis of Acute Catarrhal Jaundice					Group	Congestive Heart Failure	Outcome
		1	2	3	4	5			
81	Enlargement of liver and spleen, moderate anemia, terminal Ludwig's angina, septicemia, marked diffuse cirrhosis at autopsy	I	46	59	21	Biphasic delayed		560	
82	Enlargement of liver and spleen, ascites, moderate anemia, leukopenia, low grade fever, right hydrothorax	I	41	64	14			4100	
83	Chronic alcoholism, ascites, leukocytes 3350	M	52	62	11			2910	13100
84	Chronic alcoholism, marked ascites, psychosis, accurate collection of urine and feces not certain	M	60	75	16	Biphasic		460	5270
85	Painless jaundice for 2 weeks (possible cinchophen poisoning)	M	44	93		Biphasic prompt		380	1020
86	Jaundice clearing, feels much better							20680	25000
86	Painless jaundice for 1 month	M	30	86		Biphasic delayed		950	++
87	Improving								
87	Jaundice fading								
87	Painless jaundice for 2 weeks	I	21	80		Biphasic			
88	Improving							820	11540
88	Painless jaundice for 10 days, now receding	M	22					800	
89	Painless jaundice for 1 week preceded by acute respiratory infection	M	27	99	107	Biphasic		1120	2050
90	Improving, feels much better, jaundice almost entirely gone							2880	
90	Painless jaundice for 1 week, acholic stools, marked bil rubinuria	M	16					2180	
91	Painless jaundice following rheumatic fever, liver slightly enlarged, recovery	F	42					940	
92	Jaundice for 4 days, preceded by nausea and vomiting, complete recovery in 2 weeks	M	21	75	187	Biphasic		2270	1080
93	Mild jaundice, enlarged liver, mild psychosis	M	18	85				1980	11560
93	Feels well no visible jaundice, liver not palpable	M	53	82				1590	26820
94	Jaundice for 3 weeks	M	53					12810	18800
94	Mild epigastric distress							050	
95	Improving							2910	1500
95	Painless jaundice for 1 month, recovery	M	30					6260	13190
96	Hypertension, with coronary disease, ascites, large tender liver, slight icterus, marked orthopnea	F	58	98				5610	
97	Probable hypertension, mild pulmonary congestion, moderate enlargement of liver, small amount of ascites	M	53	98	26	Biphasic		1110	
98	Marked improvement with rest in bed and digitalis, liver smaller, ascites gone				13			0	
98	Rheumatic mitral and aortic valve defects, large, tender liver, ascites, edema, autopsy 2 months later marked chronic passive congestion of liver	F	38	76	0			1460	13290
99	Hypertension, anasarca, passive congestion of liver and spleen at autopsy	F	39		29			110	
100	Rheumatic aortic stenosis and insufficiency, probable adhesive pericardium, improving at time of estimations	M	46	75	12			0	8310
101	Hypertension, dyspnea, slight ascites, enlarged liver, not tender	F	48	81	18			0	

TABLE 1—Data on the Excretion of Urobilinogen—Continued

Case	Condition	Sex	Age	Date	Hemo globin, %	Icterus Index	Van den Bergh Reaction	Urobilinogen Excretion, Mg per Day	
								Urine	Feces
Congestive Heart Failure—Continued									
102	Hypertension, large, tender liver, ascites, orthopnea, auricular fibrillation	F	55		106	14	Delayed	35.60	
103	Mitral stenosis, enlarged, tender liver, moderate pulmonary congestion, icterus	F	38		86	27	Delayed	9.40	211.20
104	Mitral stenosis, compensation restored after digitalization, liver still palpable, no longer tender	F	25		90	24	Delayed	3.80	
105	Heart failure due to hypertension and coronary disease, liver enlarged, firm, moderately tender, slight icterus	M	63		89	21	Delayed	38.00	259.00
	Two weeks later, much improved					12		1.40	
106	Hypertensive cardiac failure, massively enlarged and tender liver, jaundice, bilirubinuria	F	68		94	25		21.90	34.80
Group 5 Miscellaneous Diseases of Liver									
107	Probably amyloid disease, very large, smooth liver, tuberculous of spine and kidney, fever, albuminuria	M	40					19.00	
108	Banti's disease, death due to bleeding of esophageal varix, autopsy diffuse fibrosis of very large spleen, liver apparently normal	M	24	8/8	75	13		13.20	
109	Toxic vomiting of pregnancy, jaundice, psychosis	F	42	8/9	75	39		102.10	
	Large amounts of dextrose (intravenous), insulin			8/10		20		133.10	
	Therapeutic abortion			8/14		11		42.00	
				8/23				62.00	
				8/27				9.10	
				2/4				4.60	
								0	
110	Much improved	M	71					Trace	
111	Syphilis, hepatic lobatum, large liver, no jaundice, hematemeses, small amount of ascites	F	41			7		1.40	
112	Syphilis, probable hepatic gummas, no jaundice or ascites	F	30		70	4		2.70	
	Syphilis, hepatic gummas with fever, no jaundice or ascites								
Group 6 Carcinoma of Peritoneum or Liver With or Without Ascites and Without Jaundice									
113	Recurrent ascites tumor cells in fluid, no jaundice	F	61		80			Trace	
114	Ascites, biopsy of nodule in abdominal wall showed metastatic carcinoma		52		90	5		Trace	
115	Autopsy primary carcinoma of left lobe of liver of cholangio type	F	49		86	8		0.15	
116	Multiple liver metastases from primary carcinoma of breast, large liver, metastases shown with thorium dioxide	F	54		68	5		1.90	
117	Primary carcinoma of stomach, enlarged, hard liver, no jaundice	M	74		71			0.70	
118	Carcinoma of stomach with multiple liver metastases at autopsy	M	63		58	11		0.48	

[illegible]

TABLE 1—Data on the Excretion of Urobilinogen.—Continued

Case	Condition	Sex	Age	Date	Hemo- globin, %	Icterus Index	Van den Bergh Reaction	Urobilinogen Excretion Mg per Day	
								Urine	Feces
Group 7 Hemolytic Jaundice—Continued									
B Acquired									
133	Hodgkin's disease for 2 years, severe anemia for 2 or 3 months, large, very tender spleen (recent infarct), macro nucleocytosis, frequent normoblasts, fragility normal, reticulocytes 38%, continuous fever Repeated transfusions, temporary improvement Spleen smaller, no longer tender, left pleural and pericardial effusions, anemia progressive, death, autopsy small area of Hodgkin's disease in liver, marked lymph node involvement, multiple pale splenic infarcts related to obliterating endarteritis, marked congestion of splenic pulp, moderate diffuse hyperplasia and marked hemosiderosis of reticular and endothelial cells	F	18	1/19 1/22 1/23 1/25 1/28 2/5 2/8 2/14 2/18 2/19 2/23	14 35 18	22	Delayed	155 00 507 00 41 00 Trace 104 00 707 10 1 10 304 70 Trace	
134	Recurrent attacks of mild jaundice and abdominal pain for 5 years, no previous anemia, no jaundice in other members of family, spleen and liver not palpable, fragility normal on several occasions, average diameter of erythrocytes 8.86 microns, polychromatophila, normoblasts, reticulocytes 15 to 29%, autohemagglutination, mass in left side of pelvis Operation, removal of ovarian cyst containing 800 cc of fluid rich in hematin, condition not improved by operation, anemia progressive, varying jaundice	M	18	2/28/35 3/2 3/2 3/5 3/9 Transfusions 3/11 3/12 3/17 Transfusions 3/20 Transfusions 3/26 Transfusions 3/29 4/4 4/5 4/5 4/8 Transfusions 4/11 4/16 4/18 4/20 4/24 4/25 4/29 4/30 5/3 5/10 5/22 6/2 7/6/35 8/20/36	32 36 30 45	12 39 39 27	Indirect Indirect	9 80 2 50 380 80 34 50 6 20 20 20 138 00 22 30 35 20 0 90 0 60 2 30 0 60	1,106 70 986 00 1,831 20 1,180 80 401 10 1,540 00 536 20 406 70 429 00 206 00 1,010 00
Splenoectomy (weight 460 Gm.), microscopic examination pulp congestion, hemosiderosis, liver normal in appearance									
Improving									
135	Feels well, appetite and strength good, slight icterus per selets 9 000 000 erythrocytes Entirely well, no icterus Probable posttraumatic hematoma in left kidney marked hematuria, icterus? serum bilirubin 0.3 per 100 cc, hematuria, also probable hematuria, recovery	M	19	69 12 6 . 19 19 10 10 23	62 48 46 40 49 53 57 56 54 60 66 70 83 70	10 10 29	Indirect	0 60	

RESULTS

Group 1 Cholecystitis and Cholelithiasis—The determinations recorded for the subjects in groups 1 A and B demonstrate that the amount of urinary urobilinogen is only slightly increased in instances of jaundice due to stone, except when the jaundice has been severe and of at least several weeks' duration or when obstruction to the outflow of bile has been complicated by acute infection in the gallbladder or biliary tract. It is important to note that in no instance was complete biliary obstruction encountered in this group, although the stools were rather frequently acholic in appearance and in some instances were reported to show negative results of qualitative tests for urobilin and urobilinogen. This lack of complete obstruction is in striking contrast to its regular occurrence in jaundice due to cancer, as reflected in the estimations to be given presently. Case 28 in particular emphasizes the importance of recognizing this distinct difference. This patient was sent to the hospital with a diagnosis of carcinoma of the head of the pancreas, a diagnosis suggested by painless jaundice of six months' duration, accompanied with considerable emaciation. However, the presence of 10 mg of urobilinogen per day in the feces even after a long period of continuous jaundice suggested the presence of a stone in the common duct, while the even larger amount in the urine was attributed to biliary cirrhosis. These diagnoses were verified at operation. A large and firmly impacted cholesterol stone was removed from the common duct. The liver was considerably enlarged and diffusely roughened. Six months later the liver was no longer palpable, and the patient appeared to be in good health. In case 36 an entirely similar condition was recognized preoperatively only because of the absence of complete obstruction in spite of long-enduring, deep jaundice. Again a large stone was removed from the common duct at operation. The same type of excretion of urobilinogen in case 40 led to the diagnosis of stone in the common duct, but at operation no stone could be found, the common duct simply being drained. In spite of this the patient died, and at necropsy a fairly large and tightly impacted stone was present in the common duct just above the ampulla.

Several of the determinations for the patients in group 1 as well as some for the following groups illustrate that the importance of the ratio of the urobilinogen in the feces to the urobilinogen in the urine must be clearly appreciated. This fact has been emphasized previously.⁵ Perhaps the best example of its importance is case 26, in which biliary cirrhosis following stricture of the common duct was noted at autopsy. The urinary urobilinogen content was only moderately elevated (39 mg per day), but when this is compared with the small amount in the feces (67 mg per day), it is evident that the value for the urine is relatively high. The same is true in cases 28, 32 and 33.

The increased excretion of urobilinogen in the urine in instances of acute cholecystitis appears to support Graham's⁶ conception of associated hepatitis. This is best illustrated in cases 25, 27, 30, 35, 37, 38 and 41. With subsidence of symptoms pointing to infection, the urobilinogen content rapidly decreases to normal levels, as noted in cases 30, 35, 37, 38 and 41. Cases 35, 37 and 38 illustrate characteristic changes in the excretion of urobilinogen which occur when a stone

5 Adler, A., and Bressel, M. Urobilinogenbestimmung in Stuhl und Harnmittels der neuen Extraktionsmethode, *Deutsches Arch f klin Med* **155** 326, 1928. Watson^{1a}

6 Graham, E. A. Hepatitis. A Constant Accompaniment of Cholecystitis, *Surg, Gynec & Obst* **26** 521, 1918

is dislodged from the common duct or when a change in its position results in release of the biliary obstruction. The latter is best noted in case 37. Here a sudden diminution of the jaundice occurred, and with this there was a great increase in the amount of urobilinogen in the feces. There was an increased amount in the urine also, probably owing to the effect of residual cholangitis on the parenchyma of the liver. It was believed that this patient had passed a stone, however, none was found in the feces, and at operation several days later a large stone was present in the greatly dilated common duct. At the time of operation the urinary urobilinogen content had decreased to an approximately normal value.

Group 2 Obstructive Jaundice Due to Neoplastic Disease of the Biliary Tract—In sharp contrast with the foregoing findings are those obtained for patients with jaundice due to neoplastic biliary obstruction, as shown in group 2. With only one exception the values in group 2 are uniformly low for both urine and feces. By comparison with the findings already given for jaundice due to stone and with those to be given later for jaundice due to hepatic disease, it is readily seen that an obstruction to the outflow of bile of this degree is probably rarely encountered in other conditions. It was realized that jaundice due to neoplasm is regularly more marked and more continuous (von Muller⁷), but the reliability of this evidence of complete obstruction for the diagnosis of neoplasm was not fully appreciated at the outset of this investigation. Thus, a diagnosis of stone in the common duct was made in case 42, chiefly because of the history of repeated previous attacks of gallstone colic. At operation carcinomatosis of the liver, with involvement of the hepatic ducts, as well as cholelithiasis, was present. Apart from the fact that this patient had been jaundiced for a considerable period, nothing suggested the diagnosis of neoplasm except the evidence of complete obstruction yielded by the estimations of urobilinogen. Later, similar instances (cases 52 and 58) were observed in which prior to the determinations of the urobilinogen, a diagnosis of stone in the common duct had been made. Because the results indicated complete obstruction, the presence of neoplasm was believed likely. At operation the gallbladder was found to contain stones, apparently supporting the first diagnosis, the common and hepatic ducts, however, were filled with tumor, microscopically adenocarcinomatous. Another illustrative case has been observed since group 2 was compiled and may be described briefly as follows. A man aged 60 had pain in the right upper quadrant of the abdomen of several weeks' duration four months before he was admitted to the hospital. The pain was intermittent and somewhat colicky. There was increasing jaundice for two months. The icterus index was 163. The urobilinogen excreted in the feces was 17 mg per day, and none was excreted in the urine. A diagnosis of neoplastic obstruction was made, and laparotomy was performed for the purpose of making a palliative anastomosis. At operation it was believed that a small neoplasm could be palpated in the upper portion of the common duct. The patient died several days later, at necropsy there appeared to be only a benign stricture of the cystic and hepatic ducts at their junction. The gross appearance was not suggestive of neoplasm. However, a small scirrhous carcinoma was revealed on microscopic examination.

Because of ascites with enlargement of the liver, the initial clinical diagnosis in case 53 was cirrhosis of the liver. The results of the determinations of urobilinogen, however, strongly suggested a carcinomatous biliary obstruction. This was corroborated at operation.

⁷ von Muller, F. Ueber Ikterus, Jahresb d schles Gesellsch f vaterl. Cult (Med Sect) 70 1, 1893.

In only one of the cases in group 2, i e, case 44, was more than 5 mg of urobilinogen found daily in the feces. In most cases the values were much lower than this, and the amount in the urine was practically negligible. In case 44 the incomplete obstruction was readily explained at necropsy by the fact that melanomatous metastases in the common bile duct, from a primary melanoma of the ear, were soft and somewhat polypoid, permitting bile to pass into the duodenum.

In the next group of cases, i e, those of jaundice due to primary hepatic disease, the findings were again in definite contrast with those already noted in the various instances of extrahepatic obstructive jaundice. As compared with jaundice due to neoplasm, the obstruction to the outflow of bile was in no instance complete, while the amount of urobilinogen in the urine was regularly higher than for the cases of uncomplicated jaundice due to stone.

Group 3 Diffuse Hepatic Disease—The cases in group 3 were divided into four parts, as indicated in table 1. With only an occasional exception, the urinary urobilinogen content in the cases in group 3 was relatively or actually markedly increased. The lack of increase in cases 65 and 69 could not be accounted for, however, necropsy in each instance revealed a cirrhotic liver which was remarkably adenomatous, and it is possible that these adenomas were functioning so far as the removal of urobilinogen was concerned, while the jaundice could be related to mechanical obstruction due to fibrosis. Since the accompanying table was compiled, two cases of severe acute catarrhal jaundice have been studied in which the amount of urobilinogen in the urine was less than 1 mg. In one of these the amount in the feces was 15 mg per day, in the other, 9 mg. It is probable that the amount of urobilinogen reabsorbed from the bowel in these instances was excessively small or at least sufficiently small so that the liver, although damaged, was capable of its disposal. In both instances the amount of urobilinogen in the feces was sufficiently large to aid materially in excluding neoplasm as the cause of the jaundice.

In only one case of parenchymal jaundice (an instance observed since the accompanying table was compiled) was the amount of urobilinogen in the feces in the low range characteristic of neoplastic obstruction. This patient, a man aged 61 years, had been given five injections of neoarsphenamine (0.15 Gm each) in the hope of improving a urinary infection. Shortly after the last of these injections he became jaundiced. The estimations of urobilinogen yielded the following data:

Date	Icterus	Urobilinogen, Mg per Day	
	Index	Feces	Urine
1/22	67	3.1	0.5
1/27	88		
2/3	101		
2/6	88	4.7	41.5
2/12	64	57.0	54.2
2/28	25	77.9	6.4
3/10	21		7.1
3/12			5.1

This case illustrates the importance of (1) evaluating even small amounts of urinary urobilinogen in the presence of high grade biliary obstruction and of (2) repeated estimation of the urobilinogen content, particularly in the feces, in doubtful cases.

In other instances of marked jaundice, such as cases 85, 89 and 90, the importance of noting the stool-urine ratio must be reemphasized.

Fluctuation in the amount of urinary urobilinogen from day to day, noted previously by Wilbur and Addis,⁸ was observed rather frequently in the foregoing instances in which more than one determination was made. Cases 62, 67, 70, 71 and 72 are illustrative.

In cases 70 and 72 the urinary urobilinogen content decreased markedly after a short period of rest in bed, without any appreciable change in the degree of jaundice. In several cases the urobilinogen content decreased to a normal value coincident with marked clinical improvement. In one of these (case 66) the presence of ascites with jaundice led to a diagnosis of cirrhosis, the use of salyrgan resulted in prompt disappearance of the ascites, and although mild jaundice persisted, the urobilinogen value rapidly decreased to normal. In another (case 71) the urobilinogen value became normal, although the liver and spleen remained considerably enlarged. These facts are mentioned since they illustrate that the urinary urobilinogen value is not always elevated in the presence of other signs of hepatic disease. At the same time, it is believed that a marked decrease, such as has been described, points to an increase in the function of the liver.

The results recorded in group 3 B are of particular interest, since they illustrate the increased rate of destruction of blood which may accompany cirrhosis of the liver. At first glance it might seem possible that the considerable increase in the urobilinogen content of the feces in these cases could be explained by at least temporary release of a biliary obstruction. Friedrich von Muller⁷ first demonstrated the increased output of urobilin following release of an obstruction due to stone or in catarrhal jaundice. Such instances are represented in the present investigation, viz., cases 35, 37, 38 and 85.

It is believed, however, that the high values noted in group 3 B were related not to fluctuations in the flow of bile but rather to an actual increase in the rate of destruction of the blood. The reason for this belief may be stated as follows. The amounts excreted in the feces were often much larger than has been noted in cases in which the release of a biliary obstruction was known to have just occurred. In fact, the values are frequently as great or greater than those to be given later for hemolytic jaundice. In some instances the increased excretion of urobilinogen occurred at a time when there was no evidence of a decrease in the degree of biliary obstruction. In case 71, in which there was exhibited the greatest increase of urobilinogen in the feces in this group, definite macrocytic anemia of a regenerative type developed during the period of increased excretion. This later disappeared as the excretion of urobilinogen markedly decreased.

The values noted in cases 70, 71 and 72 suggest that the increased destruction of blood proceeds at a variable rate.

Group 4 Congestive Heart Failure—The limited data obtained in this investigation concerning the excretion of urobilinogen in congestive heart failure demonstrate only that urobilinuria is not of constant occurrence. In the eleven patients studied it appeared that tenderness of the liver was the only finding regularly noted with an increase of urobilinogen in the urine. Weiss⁹ pointed out that urobilinuria is usually more marked when there is decompensation due to a defect in the mitral valve than when it is due to aortic incompetence. Weiss observed also that urobilinuria in heart failure is at times slight, and he said he believed that this is due either to a lack of passive congestion of the liver or to accompan-

⁸ Wilbur, R. L., and Addis, T. Urobilin. Its Clinical Significance, *Arch Int Med* 13 235 (Feb.) 1914.

⁹ Weiss, M. Ueber Urobilin und seine diagnostische Verwertung, *Wien Arch f inn Med* 20 39, 1930.

ing renal insufficiency In the foregoing instances in which the urobilinogen value was not increased in the urine (cases 99, 100 and 101) neither of these conditions appeared to have been fulfilled, and the low values in these cases cannot be explained In five instances the amount of urobilinogen in the feces was not elevated, so that in these there was no reason to consider the jaundice due to an increased destruction of blood The latter possibility was suggested by Eppinger,¹⁰ who found an increased amount in the feces in several cases of heart failure Weiss⁹ also mentioned a "tendency" to an increased excretion of urobilin in the feces in heart failure With the exception of the five determinations mentioned, which do not indicate an increased rate of blood destruction, the present investigation does not include data relative to this question The omission of estimations for the stools in the other instances is due to the difficulty in obtaining accurate collections

Group 5 Miscellaneous Hepatic Diseases—Group 5 includes various types of hepatic disease which could not be classified with the foregoing instances In the case of Banti's disease it was of interest that the liver at autopsy did not exhibit any recognizable pathologic change In spite of this, considerable urobilinogen was present in the urine, whether owing to a functional disturbance secondary to splenic disease or to anoxemia because of hemorrhage cannot be determined This observation simply indicates that urobilinuria with Banti's disease is not necessarily on the basis of hepatic cirrhosis

In none of the three cases of *hepar lobatum* in group 5 was the urobilinogen value increased for the urine In all of these cases the liver was enlarged and jaundice was absent When contrasted with case 80 in group 3 C, in which the liver was extremely small and almost completely replaced by scar tissue, the urine containing a large amount of urobilinogen, it is evident that an increase in the urobilinogen content may be expected only in an advanced stage of the disease or when the replacement of liver by gummas is widespread

Group 6 Carcinoma of the Liver or Peritoneum—The determinations in the cases in group 6 indicate that the estimation of urinary urobilinogen is of considerable value in the differentiation of ascites due to diffuse hepatic disease from that due to peritoneal carcinomatosis The determinations indicate that ordinary carcinomatosis of the liver rarely interferes with its function of urobilinogen excretion In one instance of diffuse hepatic carcinomatosis a fairly large amount of urobilinogen was present in the urine (case 121) Case 120, in which carcinomatous metastases were present in the liver and on the peritoneum, illustrates that the urinary urobilinogen value may occasionally be elevated to the range characteristic of diffuse hepatic disease such as cirrhosis In this instance necrosis was prominent in the widespread areas of tumor and may have been responsible for the hepatic damage and urobilinuria

Group 7 Hemolytic Jaundice—Thirteen cases of hemolytic jaundice were studied in addition to the cases already mentioned in which an increased destruction of blood accompanied cirrhosis of the liver In ten of these cases the criteria for the diagnosis of familial hemolytic jaundice were fulfilled, while in the other three the condition was of the acquired, or secondary, type The former are included in group 7 A and the latter in group 7 B In all but one of the instances in group 7 the excretion of urobilinogen in the feces was markedly increased The exception, case 129, was the case of a patient who was suffering principally from ulcerative colitis and in whom the hemolytic activity appeared to be quiescent

¹⁰ Eppinger, H Die hepatolienalen Erkrankungen, Berlin, Julius Springer 1920

Of particular interest in the group of subjects with hemolytic jaundice was the relatively small amount of urobilinogen in the urine in the majority of cases. In the instances in which considerable increases occurred, factors other than a simple increase in the rate of destruction of blood appeared to be significant. The question of urobilinuria as a result of "overflow" alone will be discussed in more detail in the following pages.

COMMENT

In a recent consideration of painless jaundice Ottenberg¹¹ stated that there is at present "no clinical or laboratory method of distinguishing partial or complete obstruction of the bile duct from partial or complete suppression of bile." By this he undoubtedly referred to the difficulty often encountered in distinguishing jaundice due to hepatic damage from that due to simple obstruction in the biliary tract. The

TABLE 2—Usual Range of Urobilinogen Excretion in the Common Forms of Jaundice

	Urobilinogen, Mg per Day	
	Urine	Feces
1 Jaundice due to obstruction in biliary tract		
Stone, without complications	0.6	10-250
Stone, with complications such as cholangitis, biliary cirrhosis and anemia	4.50	10-250
Neoplasm	0.03	0.5
2 Jaundice due to diffuse hepatic disease		
Cirrhosis	4.100	8-200
Cirrhosis or hepatic disease with increased blood destruction	20-200	300-1,200
Acute catarrhal jaundice	4.200	10-300
3 Hemolytic jaundice		
Uncomplicated	1.10	300-1,800
Complicated by infectious disease, severe anemia, infarction or anesthesia and during "hemolytic crises"	10-300	300-2,500

results of the present investigation indicate that a determination of the per diem excretion of urobilinogen in the urine and feces, in conjunction with other clinical data, usually makes possible the distinction of these common forms of jaundice. In general, they are characterized by urobilinogen values of the magnitude shown in table 2.

In previous investigations of obstructive and hepatic jaundice with reference to the excretion of urobilinogen, attention was given chiefly to the amounts present in the urine, and little information has accumulated concerning the variations in the urobilinogen content of the feces in these forms of jaundice. Since the early studies of Friedrich von Muller,⁷ it has been generally recognized that tests for urobilin and urobilinogen in both feces and urine are most apt to be negative when jaundice is due to neoplasm. However, there has been little recognition of the characteristic quantitative differences in the excretion of urobilinogen existing between jaundice due to neoplasm, on the one hand, and jaundice due to stone or diffuse hepatic disease, on the other.

11 Ottenberg, R. Painless Jaundice, J. A. M. A. **104** 1681 (May 11) 1935

The results of the present investigation indicate that the amount of fecal urobilinogen with the former is almost never more than 5 mg per day and that not more than a trace of urobilinogen is found in the urine, while the value for fecal urobilinogen in the latter forms was rarely less than 10 mg and in but one instance below 5 mg. In these types the amount in the urine varies with the degree of hepatic dysfunction but may be small even in the presence of a damaged liver if the amounts of bile permitted to enter the intestine are greatly reduced. Absence of urobilinogen from the urine, although a regular finding in cases of jaundice due to neoplasm, cannot be considered peculiar to this group, since it is noted also at times with varying degrees of obstructive jaundice due to stone (cases 7, 12, 13, 14 and 15) and rarely with high grade obstructive jaundice due to cirrhosis (cases 65 and 69).

In considering the findings of complete biliary obstruction, which appear to be so characteristic of jaundice caused by a neoplasm, the question at once arises as to how long the jaundice must be present before these criteria obtain. As yet this question cannot be answered, exactly, since in no instance in this study has jaundice due to neoplasm developed under observation. In several instances, however, it was of not more than two weeks' duration, and in each of these complete biliary obstruction was already present (less than 5 mg of urobilinogen per day was excreted in the feces). It is probable that the interval between the appearance of jaundice and the development of complete obstruction is short, since the onset of jaundice points to an already considerable narrowing of the common bile duct or hepatic ducts. With the progressive constriction or plugging or both which a neoplasm regularly causes, the biliary outflow is soon totally obstructed, and the traces of urobilinogen which are found in the feces thereafter are best explained as originating from bilirubin in bile-stained epithelial cells of the intestinal tract (Gerhardt,¹² Wallace and Diamond¹³ and McMaster and Elman¹⁴). The different mechanism obtaining in jaundice due to a stone, i. e., obstruction without constriction, the ensuing dilatation of the duct permitting at least occasional egress of small amounts of bile even when the stone is impacted (as in cases 28 and 40), is reflected in the excretion of urobilinogen in the feces, which in this series was never less than 9 mg.

Patients with jaundice due to neoplasm not infrequently state that the jaundice has become less intense or that it varies in intensity. This, together with a measurable reduction in the serum bilirubin, has often

12 Gerhardt, D. Ueber Urobilin, *Ztschr f klin Med* **32** 303, 1897

13 Wallace, G. B., and Diamond, J. S. The Significance of Urobilinogen in the Urine as a Test for Liver Function, *Arch Int Med* **35** 689 (June) 1925

14 McMaster, P. D., and Elman, R. Studies on Urobilin Physiology and Pathology. II The Derivation of Urobilin, *J Exper Med* **41** 513, 1925

led to the inference that there has been a partial release of the biliary obstruction. It is conceivable that this could be effected by necrosis in a tumor or a decrease in size because of some other factor¹⁵. On the other hand, unless this release were proved by the reappearance of more than traces of urobilinogen in the feces, the fluctuations of bilirubin in the blood are more readily explained by variations in the rate of the destruction of blood. Rous and Drury¹⁶ produced complete biliary obstruction in dogs and then demonstrated that the amount of jaundice was proportional to the wastage of erythrocytes. Induced hemorrhage resulted in a diminution of the jaundice, and the administration of hemolytic agents resulted in a prompt increase of the jaundice. In our cases of obstructive jaundice due to neoplasm (group 2) it will be noted that wide variations in the degree of icterus were present, although the biliary obstruction was complete in all cases but one. The icterus indexes in this group ranged from 59 to 192. One patient (case 55) stated that the jaundice had diminished markedly in the month prior to his admission to the hospital, and in support of this statement the icterus index was found to be only 67. However, the biliary obstruction was complete, since urobilinogen was lacking in the urine and feces. In addition to the direct evidence of Rous and Drury,¹⁶ indicating that there is diminished jaundice following hemorrhage (case 54 probably illustrates this), there is also reason to believe that a compensatory decrease in the rate of the destruction of blood occurs in conditions associated with cachexia, low grade infection or inactivity, even in the absence of anemia. This was indicated in paper II of this series¹⁰. In the cases of neoplastic biliary obstruction, in which the icterus index was relatively high even in the presence of anemia, such as is illustrated in case 45, two possibilities must be considered, (1) an added hemolytic factor and (2) a slower urinary excretion of bilirubin. No information has been obtained in this study to indicate the possible importance of either of these

15 One instance of this type has been observed recently. A woman aged 64 years was first seen in January 1935, when she complained of painless jaundice of three weeks' duration. The amount of urobilinogen excreted in the feces was 0.5 mg per day, and none was present in the urine. At operation carcinoma of the common duct was present. The patient survived the operation, but with persistent deep jaundice and later ascites (for fourteen months). The urobilinogen in the feces on Jan 15, 1936, amounted to 4.8 mg per day, with only a faint trace in the urine. Later, pain and tenderness developed in the right upper quadrant of the abdomen, with some rebound tenderness. On February 26 the urobilinogen content of the feces was 77.6 mg per day, 4.2 mg per day being present in the urine. These findings indicated partial relief of the biliary obstruction, but whether it was due to necrosis or to biliary fistula into the bowel remained undetermined, as permission for necropsy could not be obtained (death occurred on March 13).

16 Rous P, and Drury, D R. Jaundice as an Expression of the Physiological Wastage of Corpuscles. *J Exper Med* 41 601 1925

McMaster and Elman¹⁷ demonstrated that infection of the biliary tract in dogs was at times responsible for the local formation of urobilin. From this it was conceivable that urobilin might be present in the urine in spite of complete biliary obstruction. However, no instance has been found in the present investigation in which only the urine and not the feces contained urobilinogen. In certain instances determinations were not made on the feces, but in these the degree of jaundice was not sufficient to suggest the presence of complete biliary obstruction. The possibility is not excluded that a portion of the urinary urobilinogen was formed in the biliary tract in cases in which biliary infection was present. In one instance (case 41) this was strongly suggested by the great disparity between the urobilinogen content of the urine and that of the stool, the former being 112 mg when the latter was but 10.5 mg.

The occurrence of a marked increase in the urobilinogen content of the feces in certain cases of hepatic disease deserves particular mention. Bleichroder¹⁸ first noted that the bone marrow is usually red in cases of hepatic cirrhosis and Gauckler¹⁹ later described histologic changes in spleens from patients with cirrhosis, which he attributed to an increased destruction of erythrocytes. He emphasized also the hemosiderosis of both spleen and liver which may occur in cases of cirrhosis. This subject was reviewed by Eppinger,¹⁰ who offered considerable evidence in support of Gauckler's views and who clearly demonstrated that an increased excretion of bilirubin into the bile and of urobilinogen in the feces occurs in some cases of cirrhosis. Eppinger¹⁰ apparently believed that this increased destruction of blood was limited to those cases of cirrhosis as described by Hanot, i. e., hypertrophic cirrhosis with jaundice and splenomegaly, but without ascites. He also stated that the jaundice in patients with such a condition is often in large part hemolytic and pointed to spectacular improvement with the disappearance of jaundice following splenectomy. Of the patients with hepatic disease in group 3 B who showed an increased amount of urobilinogen in the feces, some exhibited enlargement of the liver, while in others the liver was smaller than normal. However, in each of the instances in which definite hemolytic anemia was present the liver and spleen were considerably enlarged and jaundice was present, but there was no ascites. To this extent the present findings correspond with those of Eppinger. In two cases of atrophic cirrhosis, however, the excretion

17 McMaster, P. D., and Elman, R. Studies on Urobilin Physiology and Pathology. VI. The Relation of Biliary Infections to the Genesis and Excretion of Urobilin, *J. Exper. Med.* **43** 753, 1926.

18 Bleichroder, R. Ueber Lebercirrhose und Blutkrankheiten, *Virchows Arch. f. path. Anat.* **177** 435, 1904.

19 Gauckler, E. Les modalités histologiques de l'hématolyse et le rôle de la rate dans l'évolution du pigment sanguin, *Arch. d. mal. du coeur* **1** 401, 1908.

of urobilinogen in the feces was definitely increased, ascites was present in one of these. Consequently, it does not appear that an increased destruction of blood can be regarded as a means of distinguishing a particular variety of cirrhosis. More attention should be given to determining whether the patients with cirrhosis showing an increased destruction of blood are those who are most benefited by splenectomy.

In the recent literature much interest has centered on the macrocytic anemia which may occur with cirrhosis of the liver. Eppinger¹⁰ in 1920 pointed out that a pernicious type of anemia is at times seen with cirrhosis of the liver. A striking example of this was a case reported in 1928 by Walterhofer, Plenge and Neuberger.²⁰ Wintrobe and Shumacker²¹ and Van Duyn²² have recently observed similar instances and have collected reports of others from the literature. So far as can be determined only one case of macrocytic anemia with cirrhosis of the liver has been studied with reference to the excretion of urobilinogen. This case, recently reported by van den Bergh and Kamerling,²³ has many points in common with case 71 in the present series. In both cases macrocytic anemia developed in the course of an illness characterized by jaundice, enlargement of the liver and of the spleen and a greatly increased excretion of urobilinogen in the feces and urine. While van den Bergh and Kamerling's case terminated fatally, in the case reported here the improvement was remarkable, although the liver and spleen remained enlarged and firm. The increased destruction of blood in this instance did not persist, and it will be noted that this overactivity appears to be in some degree cyclic in other cases of this type as well (cases 70 and 72). In six of the seven cases of hepatic disease with increased urobilinogen in the feces, some information as to the size and hemoglobin content of the erythrocytes was obtained. The color index was more than 1 in five of these (cases 71, 72, 73, 75 and 76), while in one instance (case 74) it was 0.8. Measurements of the average diameter of the erythrocytes were carried out in four cases with the aid of a Whipple eyepiece micrometer. The results were as follows: 8.25 microns in case 71. (Unfortunately this measurement was not made until the patient had greatly improved. Obvious macrocytosis with a

20 Walterhofer, C., Plenge, K., and Neuberger, J. Ueber einen Fall von Biermersche Anämie mit schwerer Lebererkrankung, *Deutsches Arch f klin Med* **159** 306, 1928.

21 Wintrobe, M. M., and Shumacker, H. S. The Occurrence of Macrocytic Anemia in Association with Disorder of the Liver, *Bull Johns Hopkins Hosp* **52** 387, 1933.

22 Van Duyn, J., Jr. Macrocytic Anemia in Disease of the Liver, *Arch Int Med* **52** 839 (Dec.) 1933.

23 van den Bergh, A. A. H., and Kamerling, A. W. C. S. Lebercirrhose met haemolytische anaemie en massale haematinaemie, *Nederl tijdschr v geneesk* **78** 4434, 1934.

high color index was noted at the height of the illness), 877 microns in case 72, 835 microns in case 75 and 831 microns in case 76. A number of control measurements for normal subjects yielded values varying between 74 and 79 microns. Consequently it appears that the majority of these patients who showed an increased destruction of blood with hepatic disease exhibited macrocytosis in varying degree.

The frequent presence of an increased amount of urobilinogen in the urine in hemolytic jaundice has long been recognized. The conception that this increase is due to simple "overflow" or overloading of the liver with urobilinogen is said by Eppinger¹⁰ to have originated in the Italian school, Riva and Zoja in particular championing the view that urobilinuria parallels the destruction of blood. Brugsch and Retzlaff²⁴ and later Eppinger¹⁰ emphasized that dysfunction of the liver probably plays an important rôle in the association of urobilinuria with increased destruction of blood. The experimental work of Elman and McMaster²⁵ appeared to support the earlier view, but it is doubtful whether dysfunction of the liver could be as well excluded in their experiments as it is in many instances of human hemolytic jaundice. In this regard, Mann and Bollman²⁶ have recently expressed doubt that hemolytic jaundice as seen clinically can be reproduced experimentally. Furthermore, the earlier work offered in support of the conception of simple "overflow" did not take into account the important effects of anoxemia on the liver, such as have been adequately demonstrated by Rich and his co-workers²⁷. Rich gave as his belief that the urobilinuria in hemolytic jaundice is due in part to excess (overflow) and in part to the subnormal function of the liver. The results of the present investigation indicate that the latter factor is the more important one. A marked increase in the rate of destruction of blood alone, as evidenced by an increase in the urobilinogen content of the feces, cannot be considered the cause of an appreciable increase in the amount of urobilinogen in the urine, since many instances were observed in which a large amount was present in the feces, together with other evidence of an increased destruction of blood but in which the amount of urobilinogen in the urine was small. Only four of the patients with hemolytic jaundice in group 7 exhibited a considerable amount of

24 Brugsch, T., and Retzlaff, K. Blutzerfall, Galle und Urobilin. Zur Frage der Gallenfarbstoffbildung aus Blut, *Ztschr. f. exper. Path.* **11** 508, 1912.

25 Elman, R., and McMaster, P. D. Studies on Urobilin Physiology and Pathology. V. Relations Between Urobilin and Conditions Involving Increased Red Blood Cell Destruction, *J. Exper. Med.* **42** 619, 1925.

26 Mann, F. C., and Bollman, J. L. Jaundice. A Review of Some Experimental Investigations, *J. A. M. A.* **104** 371 (Feb. 2) 1935.

27 Rich, A. R. The Pathogenesis of the Forms of Jaundice, *Bull. Johns Hopkins Hosp.* **47** 338, 1930.

urobilinuria In three of these the increases occurred during periods when factors other than a simple increase in the destruction of blood were prominent Thus, in case 133 a large amount of urobilinogen was present in the urine at the same time that symptoms and signs referable to recent splenic infarction were dominant in the clinical picture As these subsided the urobilinogen content of the urine decreased rapidly to a normal amount, although the hemolytic anemia persisted Such an instance suggests that substances from infarcts in other organs may temporarily interfere with the function of the liver A similar view was advanced by Schiller²⁸ to explain a marked increase in the urobilinogen content of the urine in a case of large hematoma due to ectopic pregnancy A case of repeated pulmonary infarction following the development of coronary thrombosis and a mural thrombus has recently been studied with reference to the excretion of urobilinogen²⁹ The attending physician noted a marked increase in the amount of urobilinogen in the urine shortly after the onset of signs and symptoms of infarct This disappeared as the patient's condition improved Subsequently another infarct occurred and at this time the amount of urobilinogen in the urine was estimated repeatedly (the data in this case are not included in the foregoing tables)

Date

3/24 Onset of signs of pulmonary infarct (pain in chest, hemoptysis, râles and friction)

3/26 Mild jaundice

3/27 Urinary urobilinogen, 75.9 mg per day

3/28 Urinary urobilinogen, 39.6 mg per day

3/29 Urinary urobilinogen, 27.5 mg per day

3/30 Patient improving

4/4 Urinary urobilinogen, 0.7 mg per day

4/1 to 4/4 Urobilinogen in feces, 224.2 mg per day

It is evident, however, that extravasation of blood which results in jaundice or an increased excretion of urobilinogen in the feces is not always accompanied with increased amounts of urobilinogen in the urine This is illustrated by case 135, in which trauma adjacent to the left kidney resulted in hematuria with hematinemia It is of interest that no increase in the excretion of bilirubin could be demonstrated in the serum, and the elevated icterus index and the patient's color were obviously due to the hematin present (readily identified by the hemochromogen spectrum) This has been spoken of as "hematin icterus," and were it not for the marked increase of the urobilinogen content of

²⁸ Schiller, W Zur Entstehung der Urobilinogenurie, Wien Arch f inn Med **12** 417, 1926

²⁹ Dr D P Head, of Minneapolis gave me the opportunity of carrying out the determinations in this instance

the feces, it would lend support to the belief of Duesberg³⁰ that hematin is not formed in the transition of hemoglobin to bilirubin. In spite of the excessive formation of urobilinogen, the amount in the urine remained normal.

In case 134 a marked temporary increase in the excretion of urobilinogen occurred after each of two laparotomies carried out with the patient under general anesthesia. There was no bowel movement for a number of days after the operation, so that both an increased resorption of urobilinogen and a disturbed hepatic function incident to the combined anoxic effect of anemia and anesthesia must be recognized as important in explaining the large amounts of urobilinogen which appeared in the urine for short periods. There is little doubt that reabsorption of urobilinogen from the bowel is in considerable measure dependent on the rate at which the feces move through the lower portion of the intestinal tract. In the presence of injury to the liver the associated urobilinuria is much more marked if constipation, intestinal obstruction or ileus exist. The following case is illustrative. A woman aged 48 had postpneumonic empyema and possibly an abscess in the lower lobe of the left lung. Chills and fever, marked anemia, ileus with distention and infrequent small bowel movements were noted. The urinary urobilinogen content was 312 mg per day, and the urobilinogen content of the feces was 9 mg per day. The latter value was doubtless low, in part because of the relatively small amount of feces collected, nevertheless, it is evident that the great majority of urobilinogen was reabsorbed from the bowel and refused by the liver.

Only one of the patients with hemolytic jaundice (case 126) exhibited considerable urobilinuria in the absence of obvious factors believed to decrease the function of the liver. It is important to note, however, that this patient had continuous marked jaundice, the icterus index varying between 43 and 94. The van den Beigh reaction was indirect, and bilirubin was not found in the urine. The marked hyperbilirubinemia, without anemia, strongly suggested that the function of the liver was disturbed, at least so far as the rate of bilirubin excretion was concerned. In striking contrast are the findings in case 132, here the reverse is noted, i. e., marked anemia without jaundice. The absence of any increase of bilirubin in the blood in spite of the greatly increased destruction of blood can be regarded as due only to an increased ability of the liver to clear the circulating blood of bilirubin and thus prevent the appearance of jaundice. In accord with this conception is the fact that the urobilinogen value did not increase for the urine in this instance, although it was greatly increased for the feces (prior to splenectomy).

30 Duesberg, R. Ueber die biologischen Beziehungen des Hamoglobins zu Bilirubin und Hamatin bei normalen und pathologischen Zustanden des Menschen. *Arch f exper Path u Pharmacol* **174** 305, 1934.

In the cases of familial hemolytic jaundice in which splenectomy was performed the effect on the excretion of urobilinogen in the feces is clearly illustrated Eppinger¹⁰ first demonstrated the marked decrease which occurs This was also observed in one case by Goldschmidt, Pepper and Pearce³¹ These investigators studied the excretion of urobilinogen shortly after splenectomy The present results are of interest because they also afford some idea of the rate of destruction of blood many months after splenectomy It appears that splenectomy in the familial type of hemolytic jaundice usually effects a prompt reduction of the urobilinogen in the feces In certain instances (case 124) the reduction is extreme, making it appear that the spleen had been practically the only site of blood destruction, in one instance, however, the amount was still considerably elevated two weeks after operation (case 131) In the five cases (cases 123, 124, 127, 131 and 132) in which an opportunity was afforded to determine the urobilinogen value a relatively long time after splenectomy the amount was normal in four cases and slightly increased in one (case 127) In the case of acquired hemolytic jaundice in which splenectomy was performed considerable clinical improvement occurred at once, however, a much longer period intervened after splenectomy before the urobilinogen value for the feces had returned to a high normal level

The results obtained with the qualitative van den Bergh reaction in this investigation agree with those of Andrewes,³² who stated as his conclusion that the value of the method is chiefly in distinguishing frankly hemolytic from frankly obstructive jaundice Biphase reactions are seen to be of most frequent occurrence, but determination as to whether biphase reaction is prompt or delayed has proved of no value in distinguishing the forms of jaundice It should be added that a purely delayed reaction cannot be considered as characteristic of hemolytic jaundice alone, since it was encountered in occasional instances of jaundice of mild degree due to stone (cases 6, 17 and 27)

SUMMARY AND CONCLUSIONS

One hundred and thirty-five instances of jaundice or hepatic disease have been investigated with reference to the per diem excretion of urobilinogen in the urine and feces The results justify the following conclusions

Jaundice due to stone is not accompanied with a considerable increase in the amount of urobilinogen in the urine unless complications are

31 Goldschmidt, S, Pepper, O H P, and Pearce, R M Metabolism Studies Before and After Splenectomy in Congenital Hemolytic Icterus, Arch Int Med **16** 437 (Sept) 1915

32 Andrewes, C H A Clinical Study of van den Bergh's Test in Jaundice, Quart J Med **18** 19, 1924

present, such as acute cholecystitis or cholangitis, biliary cirrhosis incident to persistent biliary obstruction or severe anemia. These complications are accompanied with at least a relatively marked increase, the actual amount of urobilinogen appearing in the urine being dependent to some extent on the degree of biliary obstruction and the consequent amount of urobilinogen formed in the bowel and reabsorbed from it.

With one exception jaundice due to stone and diffuse hepatic disease in this investigation was not accompanied with complete obstruction to the outflow of bile or complete cessation of the bile flow, such as is characterized by the presence of less than 5 mg of urobilinogen per day in the feces, with slight or no traces in the urine. On the other hand, this has been the regular finding in cases of jaundice due to neoplasm. In only one instance in this group, an unusual melanomatous metastasis in the common duct, was the urobilinogen content of the feces more than 5 mg per day, while the lowest value encountered in the former groups was 8.1 mg per day, the amounts as a rule exceeding 10 mg.

Diffuse hepatic disease is usually characterized by a marked increase of urobilinogen in the urine, some of the instances of idiopathic diseases of the liver in the group of patients with cirrhosis were accompanied with evidence of an increased destruction of blood, i. e., an increase of the urobilinogen content of the feces and regenerative anemia, often macrocytic.

In hemolytic jaundice increases in the amount of urinary urobilinogen could not be correlated with increased destruction of blood, but for the most part it occurred when other factors, which are believed to disturb the function of the liver, also were present. The urobilinogen content of the feces was usually increased to a marked degree, in the majority of cases decreasing rapidly after splenectomy.

CLINICAL SIGNIFICANCE OF THE CREATINE RESERVE OF THE HUMAN HEART

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The first reported estimations of the creatine content of human cardiac muscle seem to be those of Constabel,¹ who analyzed a total of 38 hearts and obtained values ranging from 60 to 188 mg per hundred grams for the concentration in the left ventricle. No relation to age or sex was observed, but hearts with fatty and other degenerative changes showed significantly lower values than those that were more nearly normal. In general the creatine concentration was about 10 per cent lower in the right than in the left ventricle.

In 1929 Bodansky, Schwab and Brindley² reported analyses of various muscles, including the myocardium of the left ventricle of a patient with generalized myositis fibrosa. The heart, which microscopically revealed certain abnormalities, such as enlargement of the fibers, granular cytoplasm, mononuclear inflammatory cells and increased fibrosis, contained 159 mg of creatine per hundred grams of tissue. There were no data with which to compare this result but Constabel's, which were considered low. At the first opportunity, therefore, hearts were obtained from three healthy young adults who had met death by accident, autopsy being performed less than an hour post mortem. Analysis by the method of Rose, Helmer and Chanutin³ gave values for creatine of 261, 257 and 220 mg, respectively (Bodansky⁴).

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1 Constabel, F. Ueber den Kreatingehalt des menschlichen Herzmuskels bei verschiedenen Krankheitszustanden, *Biochem Ztschr* **122** 152, 1921

2 Bodansky, M., Schwab, E. H., and Brindley, P. Creatine Metabolism in a Case of Generalized Myositis Fibrosa, *J Biol Chem* **85** 307, 1929. Schwab, E. H., Brindley, P., Bodansky, M., and Harris, T. H. Generalized Myositis Fibrosa, *Ann Int Med* **6** 422, 1932

3 Rose, W. C., Helmer, O. M., and Chanutin, A. A Modified Method for the Estimation of Total Creatinine in Small Amounts of Tissue, *J Biol Chem* **75** 543, 1927

4 Bodansky, M. Creatine in Human Muscle, *J Biol Chem* **91** 147, 1931

From these meager references⁵ it is apparent that little attention was given to the subject as long as creatine was known merely as a constituent of muscle without a well defined physiologic rôle. However, interest was soon aroused as the result of a succession of important discoveries which showed, first, that a considerable proportion of the creatine exists in muscle as an ester of phosphoric acid (Eggleton and Eggleton⁶ and Fiske and Subbarow⁷), that the energy for muscular contraction is primarily derived from the hydrolysis of phosphocreatine (Lundsgaard⁸) and that within certain limits the newer concepts of the chemistry of muscle activity, based partly on these discoveries, could be applied to the metabolism of cardiac muscle (Clark, Eggleton and Eggleton⁹).

For obvious reasons a complete study of the relation of the creatine content to the metabolism of cardiac muscle in health and disease on human material is out of the question. The rapid hydrolysis and disappearance of glycogen and phosphocreatine which result from even slight alterations of the *in vivo* conditions preclude their estimation after death, hence those who have attempted to study the problem in man have confined themselves to the determination of the total creatine content, the two notable contributions along this line being those of Cowan¹⁰ and Seecof, Linegar and Myers¹¹.

Cowan¹⁰ reported analyses of 80 hearts, 48 of which were classified as normal, as they showed comparatively little change anatomically (cloudy swelling, brown atrophy and sclerosis). Death was due to a variety of causes, such as pneumonia, empyema, tuberculosis, carcinoma, anemia and diabetes. The average creatine concentration was 202 mg per hundred grams of tissue, with a standard deviation of 37 mg. Evidence of cardiac decompensation existed in 17 cases. In these the average was 147 mg, with a standard deviation of 37 mg. In a third

5 Constabel¹ Bodansky, Schwab and Brindley² Bodansky⁴

6 Eggleton, P., and Eggleton, G. P. The Inorganic Phosphate and a Labile Form of Organic Phosphate in the Gastrocnemius of the Frog, *Biochem J* **21** 190, 1927

7 Fiske, C. H., and Subbarow, Y. The Nature of the "Inorganic Phosphate" in Voluntary Muscle, *Science* **65** 401, 1927, Phosphocreatine, *J Biol Chem* **81** 629, 1929

8 Lundsgaard, E. Untersuchungen über Muskelkontraktionen ohne Milchsäurebildung, *Biochem Ztschr* **217** 162, 1930

9 Clark, A. J., Eggleton, M. G., and Eggleton, P. Phosphagen in the Perfused Heart of the Frog, *J Physiol* **75** 332, 1932

10 Cowan, D. W. The Creatine Content of the Myocardium of Normal and Abnormal Human Hearts, *Am Heart J* **9** 378, 1934

11 Seecof, D. P., Linegar, C. R., and Myers, V. C. The Difference in Creatine Concentration of the Left and Right Ventricular Cardiac Muscles, *Arch Int Med* **53** 574 (April) 1934

group of 15 hearts of subjects who had shown clinical manifestations of heart disease and pathologic evidence of myocardial damage, cardiac hypertrophy or some other disorder, the creatine concentration of the left ventricle averaged 165 mg, with a standard deviation of 30 mg. According to Cowan,¹⁰ his results suggested that the "reserve" of the heart closely parallels its creatine content.

Seecof, Linegar and Myers¹¹ compared the creatine concentrations of the left and right ventricles. They analyzed a total of 102 hearts, employing in each case blocks of tissue from anatomically similar locations. In 84 the range for the left ventricle was from 116 to 369 mg (average, 211 mg). The range for the right ventricle was from 93 to 283 mg (average, 148 mg). Except in the heart of a newborn infant, the concentration was invariably greater in the left than in the right ventricle, the average difference being 63 mg, or 30 per cent, using the left ventricle as the standard.

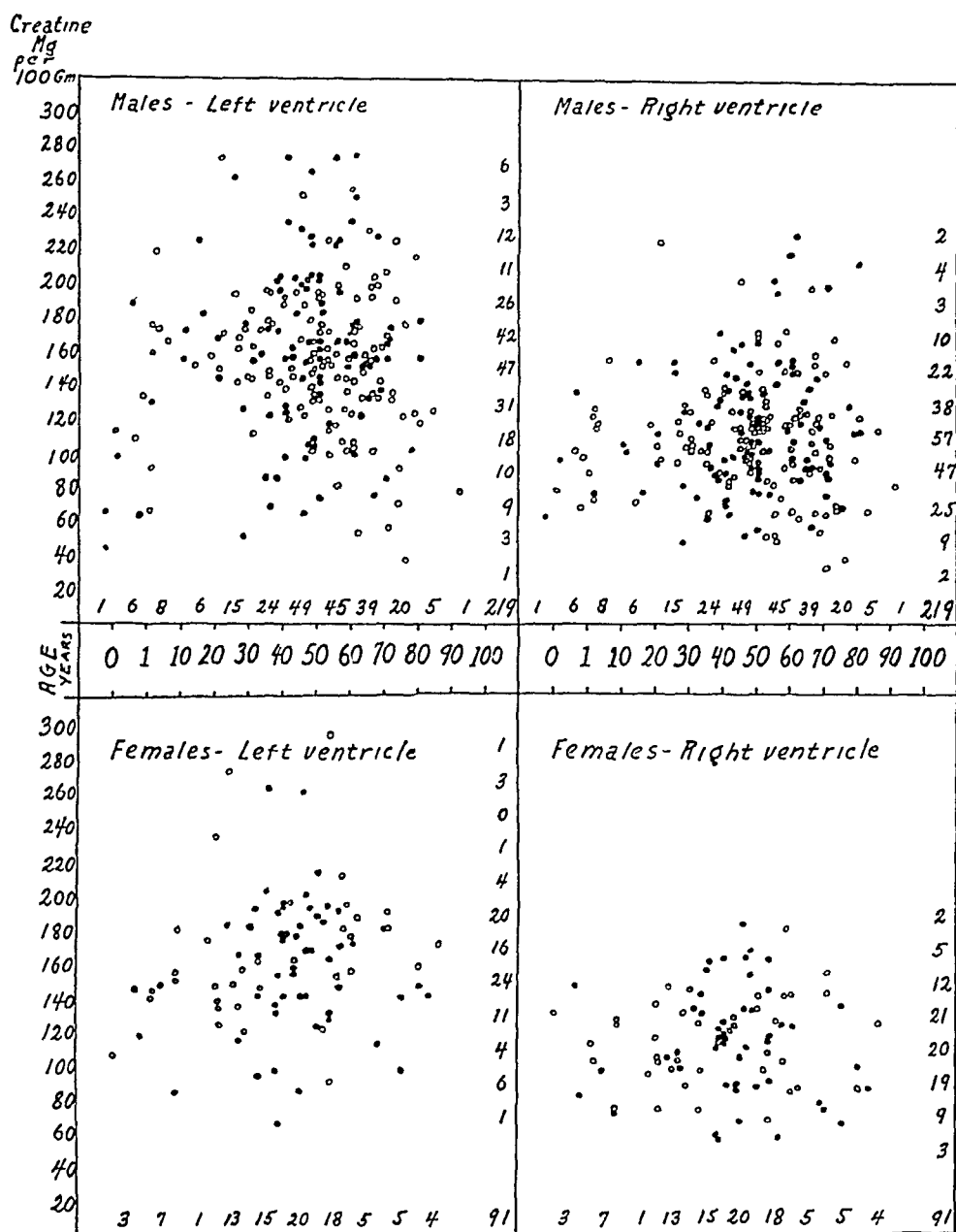
The present report is based on the analyses of the left and right ventricles of 310 hearts, the largest series so far reported.¹² In addition, data have been obtained for the papillary muscles of 52 hearts. The cardiac samples were taken from approximately identical locations, in accordance with the suggestion of Seecof, Linegar and Myers.¹¹ Most autopsies in this institution are performed within four or five hours after death, seldom later than twenty-four hours. In the interval the corpse is kept in a morgue maintained at 3 or 4 C. For this investigation analyses were not made when the autopsy was unduly delayed. Usually the tissues were promptly subjected to the preliminary stages of analysis, but occasionally a delay of several hours was unavoidable, during which time the specimens were kept in stoppered bottles in a refrigerator. Our experience has confirmed the observations of others that aseptic autolysis of short duration has no significant effect on the total creatine content of tissues. For the estimation of creatine the method of Rose, Helmer and Chanutin³ was used, every detail of the procedure being carefully controlled.¹³

12 After approximately half this work was completed Herrmann and his co-workers independently analyzed a number of left ventricles, some of which were in our series of autopsies. Their results were included in a discussion entitled "Some Biochemical Factors of Heart Failure" (South M J 29 386, 1936).

13 In connection with various studies in this laboratory¹⁷ a large number of creatine estimations have been made for a relatively uniform statistical population (normal rats, heart and other tissues). For over two years the practice has been to carry out the analyses of the human hearts in company with a sufficient number of tissues of normal rats, especially cardiac tissue, so that any significant technical error in any set of determinations would be readily detected.

RESULTS

In evaluating the results it is to be realized that the 310 hearts represent a heterogeneous and complex statistical population, but in order to present a general view of the data and their variability and



Creatine concentrations of the left and of the right ventricle, arranged according to the age and sex of the subjects. The white circles represent white subjects and the black circles Negroes. The numbers for each age group are given along the abscissa, the numbers along the ordinate indicate the distribution of cases for each interval of 20 mg in creatine concentration.

to bring out grossly the relation of the right to the left ventricle and such other differences as may conceivably be related to age, sex and race, the data for the group as a whole are represented in the accom-

panying figure Ten of the 310 hearts were of new-born infants or of infants less than 1 year old These will be considered separately The remaining 300 hearts were of subjects whose ages ranged from 1 to 92 years In these the creatine concentration varied from a minimum of 38 to a maximum of 295 mg, the average being 159.2 mg The concentration in the right ventricle likewise varied within wide limits, from 38 to 230 mg with an average of 114 mg

TABLE 1—*Creatine Concentration of the Heart*

	Mg of Creatine per 100 Gm of Tissue			Standard Deviation
	Maximum	Minimum	Average	
212 males				
Left ventricle	275	38	157.10	45.56
Right ventricle	230	38	114.40	34.71
Difference and standard error of the difference of the two means			42.7 ± 3.00	
P (Fisher ¹⁴)			<0.01	
88 females				
Left ventricle	295	67	163.80	40.11
Right ventricle	184	58	114.60	28.46
Difference and standard error of the difference of the two means			49.2 ± 5.20	
P (Fisher ¹⁴)			<0.01	

TABLE 2—*Classification of Patients*

Group		Number of Patients		Conditions Included
		Male	Female	
1	Congestive heart failure	50	20	
2	Cardiac hypertrophy (>400 Gm in males, >350 Gm in females)	39	16	Syphilitic aortitis, hypertension, subacute bacterial endocarditis, chronic nephritis, cerebral hemorrhage, etc
3	Clinical or pathologic evidence of heart disease moderate to severe degeneration of myocardium, not included in groups 1 and 2	51	27	Pericarditis, chronic nephritis, peritonitis, tuberculosis, diabetes, carcinoma, pellagra, pneumonia, diphtheritic myocarditis, etc
4	No evidence of heart disease, minimal degenerative changes of myocardium	40	15	Meningitis, tuberculosis, carcinoma, nephritis, eclampsia, peritonitis, suicide, etc
Total		180	78	

Of the 300 subjects over 1 year of age, 212 were males and 88 females Although there appeared to be little difference between the averages for the two sexes, nevertheless, the data for each group were tabulated separately (table 1) The results were further arranged according to the predominant clinical and pathologic observations Thus 50 males definitely died of congestive heart failure, in 39 there was marked cardiac hypertrophy For reference a summary of the four subdivisions is given in table 2, while the data for each group are outlined in table 3 In these tabulations only those cases were included in

which both the clinical and the pathologic data were essentially complete. Borderline cases, or cases in which the information was incomplete or uncertain, were omitted from these tables.

TABLE 3—*Creatine Reserve of Myocardium and Comparison of Left and Right Ventricles in Various Groups*

		Mg of Creatine per 100 Gm of Tissue			Standard Deviation
		Maximum	Minimum	Average	
Group 1 (congestive heart failure)*					
50 males					
	Left ventricle	265	38	139.1	53.86
	Right ventricle	218	35	103.0	35.38
	Difference			36.1 ± 9.1	
	P (Fisher ¹⁴)			<0.01	
20 females					
	Left ventricle	295	51	146.1	53.57
	Right ventricle	169	49	108.0	35.11
	Difference			38.1 ± 14.3	
	P (Fisher ¹⁴)			<0.01	
Group 2 (cardiac hypertrophy)					
39 males					
	Left ventricle	237	81	145.6	34.80
	Right ventricle	169	49	109.0	22.70
	Difference			36.6 ± 6.6	
	P (Fisher ¹⁴)			<0.01	
16 females					
	Left ventricle	260	90	167.0	41.40
	Right ventricle	184	69	111.0	31.06
	Difference			56.0 ± 12.9	
	P (Fisher ¹⁴)			<0.01	
Group 3					
51 males					
	Left ventricle	265	58	165.0	47.50
	Right ventricle	223	52	116.0	37.90
	Difference			49.0 ± 8.5	
	P (Fisher ¹⁴)			<0.01	
27 females					
	Left ventricle	264	98	168.0	35.50
	Right ventricle	160	59	113.0	25.10
	Difference			55.0 ± 8.4	
	P (Fisher ¹⁴)			<0.01	
Group 4					
40 males					
	Left ventricle	273	97	174.7	29.60
	Right ventricle	212	84	127.8	20.10
	Difference			46.9 ± 6.5	
	P (Fisher ¹⁴)			<0.01	
15 females					
	Left ventricle	236	140	171.3	28.60
	Right ventricle	162	87	123.7	23.30
	Difference			47.6 ± 9.4	
	P (Fisher ¹⁴)			<0.01	

* Heart weights in grams: group 1, males, minimum 280, maximum 1,060, average 546.5; females, minimum 330, maximum 720, average 499. Group 2, males, minimum 400, maximum 680, average 480; females, minimum 350, maximum 600, average 423.

From the data in tables 1 and 3 it will be noted that the creatine concentrations of both ventricles varied within wide limits, the variability being greatest for the group of subjects with congestive heart failure and least for the group in which there was no evidence of heart dis-

ease In the group with heart failure the average concentrations for the two ventricles were lower than the corresponding values for the entire population and especially for groups 3 and 4 As a rule the concentration was greater in the left than in the right ventricle, as shown by the difference between their means Indeed, the probability that these differences were not due to chance exceeds 100:1 ($P = < 0.01$) for all groups While this may be taken to predict the probable outcome for any comparable series of analyses, it should not be assumed that the result in any given case can be predicted with any confidence, for even among adults there were frequent exceptions to the rule of proportionality for the creatine content of the two ventricles (table 6)

The concentration in the left ventricle was somewhat higher for the females than for the males However, the difference cannot be regarded as statistically significant ($t = 1.17$, $P = 0.2$ or 0.3) In about two

TABLE 4—*Distribution of Concentrations of Creatine in the Left Ventricle Above 200 Mg and Below 120 Mg*

Creatine Concentration, Mg per 100 Gm	Total Number of Cases	Group 1	Group 2	Group 3	Group 4	Unclassified
260-295	11	2	1	5	3	0
240-259	2	0	1	1	0	0
220-239	13	2	3	4	3	1
200-219	15	2	1	4	7	1
Totals	41	6	6	14	13	2
100-119	18	10	6	2	0	0
80-99	15	5	5	4	1	0
60-79	8	7	0	1	0	0
Below 60	4	3	0	1	0	0
Totals	45	25	11	8	1	0

fluids of the cases the creatine concentrations for the left ventricles were within the limits 159.2 ± 33.7 mg There were indeed only 41 cases in which the concentration exceeded 200 mg and 45 in which it was less than 120 mg Classification of these results according to the predominant clinical and pathologic observations (table 4) revealed the following interesting facts Of the 41 subjects who showed a concentration greater than 200 mg, only 6 belonged to group 1 and 6 to group 2 The greater number represented subjects belonging to groups 3 and 4 On the other hand, of the 45 persons in whom the creatine concentration was low (120 mg or less), 36 were in groups 1 and 2 and only 9 in groups 3 and 4 These findings may be considered as partly supporting Cowan's suggestion that the functional reserve of the heart is related to its creatine reserve However, a more critical analysis of the data from this standpoint will be attempted shortly

L/R Ratio—In table 5 are given the ratios of the creatine concentration for the left (L) and the right (R) ventricle It will be observed

that for the males the average L/R values were somewhat lower in groups 1 and 2 than in group 4, while in group 3 the ratio was highest. This may be due to the fact that the last group included a considerable proportion of subjects with pneumonia, in which there was often present moderate or severe degeneration of the myocardium, the classification in group 3 being based on this finding. Moreover, in pneumonia, as will be seen, the creatine concentration of the right ventricle tends to be lowered. In the females cardiac hypertrophy (group 2) was much less often associated with creatine depletion from the left ventricle than in males. This point will be referred to again later.

For the 212 males the average difference between the two ventricles was 43 mg (maximum, +134, minimum, -27 mg). The L/R ratios averaged 1.38 (maximum, 2.87, minimum, 0.73), with a standard deviation of 0.35. For the 88 females the average difference between the ventricles was 46.5 mg (maximum, +186, minimum, +6 mg). The

TABLE 5 —*Ratios of Creatine Concentration in Left and Right Ventricles (L/R)*

Group	Male		Female	
	Number of Cases	L/R (Average)	Number of Cases	L/R (Average)
1	50	1.35	20	1.35
2	39	1.34	16	1.50
3	51	1.42	27	1.49
4	40	1.37	15	1.38
Total*	212	1.38	88	1.43

* This comprises all the autopsies on adults and includes a number of cases not classified in the four groups.

L/R ratios averaged 1.43 (maximum, 2.7, minimum, 1.05), with a standard deviation of 0.336. As these figures showed striking variability, it seemed of interest to inquire whether the more divergent results were in any way associated with definite clinical or pathologic manifestations. Accordingly the results were classified as in table 6, grouping on the one hand those cases in which the L/R ratios exceeded 1.6 (i.e., in which there was a relative impoverishment of the myocardium of the right ventricle) and, on the other hand, those cases in which the L/R ratio fell below 1.1 (i.e., in which there was relative creatine impoverishment of the left ventricle). Since we had observed low creatine values for the right ventricle in cases of lobar pneumonia and other types of severe pulmonary involvement, cases of these conditions are grouped separately in the table, except when the figures are enclosed in parentheses. From table 6 it will be noted that in 31 of the 69 cases in which there was a relative loss of creatine from the right ventricle there was pneumonia or other severe involvement of the lungs (tuberculous pneumonia, conglomerate tuberculosis or severe pulmonary edema). As there were a total of 67 cases in which a com-

parable degree of pulmonary involvement was present, it follows that in 46 per cent of these there occurred a relative loss of creatine from the right ventricle. This is to be compared with 12 per cent, representing a similar relation in the remaining 233 cases. From these data, which are admittedly meager, it seems that in persons with pneumonia and to some extent in other types of severe pulmonary disease a lowered creatine reserve in the right ventricle occurred about four times as often as in the remaining autopsy population. It may be further observed that in 7 of 12 cases in which death was due to lobar pneumonia the L/R ratio exceeded 1.6, this occurred in 10 of 28 cases of bronchopneumonia.

A lowered creatine reserve in the right rather than in the left ventricle is not an uncommon finding in cases of congestive heart failure.

TABLE 6—*Distribution of L/R Ratios Above 1.6 and Below 1.1*

Concentration of Creatine		Number of Cases	Group 1	Group 2	Group 3	Group 4	Pneu- monia	Other Severe Pulmonary Conditions
Left Ventricle	Right Ventricle							
Above 2.6		3	1	0	0	0	1	1
2.4-2.59		5	0	0	0	0	5	0
2.2-2.39		3	0	0	1	0	1	1
2.0-2.19		5	1	0	0	1	2	1
1.8-1.99		20	5	2	4	3	5	1
1.6-1.79		33	6	5	7	2	10	3
Total		69	13	7	12	6	24	7
1.0-1.09		21	14	3	2	2	(1)	0
0.8-0.99		12	8	1	2	1	(1)	0
0.73-0.79		2	1	0	1	0	0	0
Total		35	23	4	5	3	(2)	0

Indeed, in 13 of a total of 70 patients (50 males and 20 females) this was noted. More often, however, the L/R ratio tends to be low (relative depletion of creatine from the left ventricle), as indicated in table 6. Of the 35 cases in which the L/R ratio was less than 1.1, 23 were in group 1 (congestive heart failure). Only 2 of the 35 subjects had pneumonia (lobar), both being classified in group 3 on the basis of the microscopic picture.

The results therefore indicate that such factors as may be expected to contribute to strain or exhaustion of either the left or the right ventricle are often associated with a lowered creatine concentration of the corresponding portion of the myocardium. A more adequate appreciation of the constancy and significance of the changes may be gained, however, from the data outlined in table 7. In this table are given the values of the probabilities of the nonsignificance of the difference of the means, these having been calculated for each set of pairs. This table thus affords a ready means of comparing the average myocardial creatine reserve of any group with that of any other.

To illustrate, in the case of the left ventricle (males), comparison of group 1 (congestive heart failure) with group 2 (cardiac hypertrophy, compensated heart disease and other disorders) gives the value of 0.5 for *P* which denotes that no real significance can be attached to the differences between the means for these groups (see also table 3), nor can the value 0.05 obtained on comparing groups 1 and 3 and 2 and 3 (left ventricle, male) be considered of statistical significance, even though it represents a 20:1 probability that the differences were not due to chance. On the other hand, the *P* value of 0.02 (50:1 probability) derived from the means for group 1 and the total male population may be accepted as significant, as may certainly the values of <0.01 in columns 5 and 9. From these it is apparent that there was definitely a significant difference between the mean concentrations of creatine of the subjects with heart failure and those without heart disease (group 4) and that there was also a real difference between the latter

TABLE 7—Comparison of Various Groups, as Shown by the Values of *P**

	Males								Females							
	Left				Right				Left				Right			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Total	0.02	0.2	0.4	0.20	0.05	0.4	0.7	0.90	0.1	0.8	0.7	0.5	0.4	0.7	0.8	0.3
1		0.5	0.05	<0.01		0.4	0.05	<0.01		0.2	0.1	0.1		0.8	0.6	0.2
2			0.05	<0.01			0.4	<0.01			>0.9	0.4			0.9	0.4
3				0.3				0.1				0.8				0.2

* For an explanation of the use of the letter *P* here see text

and those with cardiac hypertrophy (group 2). But, as has been stressed in discussing the differences between the left and the right ventricle, these calculations, while predicting the probable results in similar comparisons, do not necessarily determine with any degree of assurance the outcome in any single case, as it is not uncommon, even in congestive heart failure, for the creatine reserve of the myocardium to remain unchanged or even at levels well above the average.

The data in table 7 suggest, moreover, a difference between males and females. It will be observed that the values of *P* derived from the comparisons of group 1 with the total female population and with group 4 denote only a 10:1 probability that the differences between the means were not due to chance. Even less significant differences are indicated by the values of *P* based on the following comparisons: left ventricle, groups 2 and 4, and 3 and 4; right ventricle, all combinations. However, this disparity between the sexes may be more apparent than real. Because of the wide range of variability (note the standard deviations for group 1, male and female, table 3) a greater number of females may have yielded value for *P* comparable to those obtained for the males. When the variation of individual observations is small,

a small group of observations may suffice and indeed it is because Fisher's calculations¹⁴ may be applied to small numbers of experiments or observations that they have found such general use

In cardiac hypertrophy the creatine concentration of the left ventricle was comparatively higher in females than in males (table 3). Although there was a greater incidence of syphilitic aortic disease in the males, while in the females there was a greater proportion of hypertensive heart disease, no definite correlation was possible between these factors and the creatine reserve of the myocardium, nor was it possible to establish any relation, either in group 2 or in group 1, with regard to therapeutic management (digitalis, various diuretics and other drugs) or to the administration terminally of dextrose, epinephrine, caffeine sodiobenzoate and other drugs. In the absence of definite correlations, the suggestion is offered tentatively that the lower creatine concentration of the myocardium for the males in group 2 as compared with that of the females in group 2 may be related not to heart disease primarily but to other associated or superimposed factors. Thus the added strain on the heart due to physical work may conceivably be responsible, in part, for the more frequent reduction of the myocardial reserve of creatine in men with heart disease than in women. In this connection it is relevant to refer to the recent observation of Chanutin and Ludwig¹⁵ that in cardiac hypertrophy produced in partially nephrectomized hypertensive rats, the creatine content increases in approximately direct proportion as the size of the heart increases, hence the creatine concentration remains fairly constant.

Papillary Muscles—In 52 analyses the following results were obtained

	Mg. of Creatine per 100 Gm.		
	Maximum	Minimum	Average
Left ventricle	272	104	167.0
Right ventricle	223	52	115.3
Papillary muscle (left ventricle)	203	85	139.4

The creatine concentrations of the papillary muscles appeared to be intermediate between the concentrations in the two ventricles. In fact, this relation held in 43 of the 52 hearts analyzed. In 2 cases the concentrations were somewhat greater than that in the left ventricle, while in 7 it was less than that in the myocardium of the right ventricle. The concentration of creatine in the papillary muscle obtained from the right side was usually less than that from the left side.

¹⁴ Fisher, R. A. Statistical Methods for Research Workers, ed. 4, Edinburgh, Oliver & Boyd, 1932.

¹⁵ Chanutin, A. and Ludwig, S. Experimental Renal Insufficiency Produced by Partial Nephrectomy. IV. Creatine Content of Hypertensive Hypertrophied Hearts of Rats Fed Whole Dried Meat, Arch. Int. Med. **57**: 887 (May) 1936.

Creatine Concentration of the Heart in Infancy—In the newborn somewhat lower values were obtained than in the case reported by Seecof, Linegar and Myers¹¹. In agreement with their observation the concentration was lower in the left than in the right ventricle

	Mg of Creatine per 100 Gm	
	Left	Right
5 to 6 month fetus	45	66
Female new born	108	131
Male new born	78	112

In a 7 week old infant the relation of the concentrations was 98/97. In 6 others who died during the first year of life the creatine concentrations varied from 62 to 189 mg in the left ventricle and from 69 to 146 mg in the right. The L/R ratio in 1 infant was 1, in 4 others it exceeded 1, in a child with bronchopneumonia it was $133/69 = 1.9$.

COMMENT

Without unnecessarily belaboring the subject, it may be stated briefly that cardiac activity depends on an adequate supply of oxygen and sufficient reserves of glycogen, phosphocreatine and such other components as may participate in the energy transformations of the myocardium. The relative sensitivity of the heart to oxygen want, its low ability, compared to skeletal muscle, to acquire an oxygen debt and the tendency to a rapid loss of glycogen and an increase in the amount of lactic acid which accompanies anoxemia, from whatever cause, have been established by recent investigations¹⁶. This leaves little doubt that in considering the problems of circulatory failure the biochemical aspects loom large and cannot be neglected. At the same time it may be appropriate to stress that the conditions associated with heart failure, clinically, may be sufficiently different from those in the experimental animal to render uncertain such assumptions as may be based entirely on experimental data.

The specific point in question is the relation of heart failure to the creatine reserve of the myocardium. As has been shown previously,¹⁷

¹⁶ Katz, L. N., and Long, C. N. H. Lactic Acid in Mammalian Cardiac Muscle, *Proc Roy Soc, London*, s B **99** 8, 1926. Hines, H. J. G., Katz, L. N., and Long, C. N. H. *ibid* **99** 20, 1926. Katz, L. N., Kerridge, P. T., and Long, C. N. H. *ibid* **99** 26, 1926. Himwich, H. E., Goldfarb, W., and Nahum, L. H. Changes of the Carbohydrate Metabolism of the Heart Following Coronary Occlusion, *Am J Physiol* **109** 403, 1934. Meakins, J. C. Modern Muscle Physiology and Circulatory Failure, *Ann Int Med* **6** 506, 1932.

¹⁷ Bodansky, M. The Effect of Thyroid and Thyroxine on the Concentration of Creatine in the Heart, Muscle, Liver, and Testes of the Albino Rat, *J Biol Chem* **109** 615, 1935. Bodansky, M., Pilcher, J. F., and Duff, V. B. *J Exper Med* **63** 523, 1936. Bodansky, M., and Duff, V. B. *Proc Soc Exper Biol & Med* **34** 307, 1936, *Endocrinology* **20** 537 and 541, 1936.

heart failure in the hyperthyroid rat is associated with a marked reduction of the creatine concentration of the myocardium. From an initial value of about 190 mg, which closely approximates the normal concentration in man, the creatine concentration may be reduced to 90 mg, but rarely below this level, because circulatory failure usually supervenes when the creatine reserve has been reduced to about 50 per cent of normal. Not only are the results such as to justify a prediction of the probable outcome for any similar series of experiments, but because of their relative uniformity a significant loss of creatine may be predicted with reasonable confidence for any single experiment, there having been essentially no exceptions to the rule among more than 300 rats treated with large doses of thyroid or thyroxin. This stands in marked contrast to the results in cases of clinical heart failure described in the present paper. While the values for P reveal significant differences between the means of certain groups (subjects with heart failure compared with the entire population or with the subjects in whom there was no evidence of heart disease), individual results lacked uniformity and were hence unpredictable. In short, each case of heart failure seems to be a law unto itself. The conditions clinically are apparently too complex to permit the ready and simple definition that may be justified in experimental heart failure, in which, on the basis of our work and the work of others, it seems that the glycogen and phosphocreatine mechanisms are primarily affected and that the depletion of creatine follows the loss of phosphocreatine. Available information and the examination of our own clinical data in relation to therapeutic measures and other factors do not permit an explanation of the diversity of the results in heart failure, the maintenance of the creatine reserve at a comparatively high level in some cases and its reduction in others. It does appear, however, that such factors as may be expected to increase the load on either the right or the left ventricle, thereby leading to exhaustion, are often associated with a lowered creatine reserve of the corresponding portion of the myocardium.

SUMMARY

Determinations have been made of the creatine concentration of the right and of the left ventricle of 310 hearts obtained at autopsy. In addition, the papillary muscles of 52 hearts were analyzed.

The data have been treated statistically and correlated, as far as possible, with the clinical manifestations and pathologic observations

TREATMENT OF ESSENTIAL AND MALIGNANT HYPERTENSION BY SECTION OF ANTERIOR NERVE ROOTS

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Since no medical treatment is known which will lower the level of the blood pressure of a patient suffering from essential hypertension more than temporarily, surgical measures deserve trial. That it is desirable to reduce the level of the blood pressure in such a patient has not always been conceded. Clinical observation, however, suggests that continued hypertension of itself causes vascular disease. Temporary reduction of an abnormally high pressure by means of drugs, such as sodium thiocyanate or colloidal sulfur, has not been observed in this clinic to produce symptoms and signs of inadequate gaseous metabolism or disturbances of tissue nutrition. These might have been expected were hypertension a compensatory mechanism serving some useful purpose. Nor have recent observations¹ supported the belief of Traube that the arterial pressure must be abnormally elevated to maintain an adequate perfusion of blood through the kidneys. Reduction, especially of the diastolic pressure, might conceivably interfere with the blood supply of the heart in cases of coronary sclerosis and so predispose to attacks of angina pectoris. This has not been observed so far as we are aware. It appears that no contraindications have been established, though they may well exist, for reduction of the arterial pressure of patients suffering from essential hypertension. The purpose of section of the anterior nerve roots is, then, to reduce the abnormal pressure by removing partially the nervous control of a portion of the splanchnic area, including the abdominal wall.

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1 Page, I H. The Effect on Renal Efficiency of Lowering Arterial Blood Pressure in Cases of Essential Hypertension and Nephritis, *J Clin Investigation* **13** 909, 1934

POSSIBLE MECHANISM OF THE LOWERING OF BLOOD PRESSURE BY
SECTION OF THE ANTERIOR ROOTS

It has long been recognized among physiologists that the vessels of the splanchnic region are of importance in the maintenance of the blood pressure level. The evidence for this belief is varied. Closure of the aorta below the level of the renal vessels produces only a slight rise in the blood pressure. The pressure is elevated slightly more if the subclavian and carotid arteries are simultaneously closed. If, however, the aorta is clamped directly above the diaphragm, eliminating the splanchnic region from the circulation, a marked rise in pressure occurs (von Bezold,² Ludwig and Thiry³). In 1875 Litten⁴ noted that ligation of the superior mesenteric artery of the dog resulted in a prompt rise in the arterial pressure, which frequently persisted for several hours. Longcope and McClintock⁵ observed in their experiments that hypertension resulted when the superior mesenteric artery and the celiac axis were constricted. Permanent hypertension was not obtained, probably owing to the development of collateral circulation. Von Bezold² showed that in curarized rabbits electrical stimulation of isolated segments of the cord resulted in a rise in the blood pressure, the extent varying with the segment stimulated. Stimulation of segments in the cervical region was without effect, but below the third thoracic segment both the heart rate and the arterial pressure were markedly increased. Bradford⁶ stimulated the anterior nerve roots in dogs within the dura and found that while the fourth and fifth thoracic and third lumbar roots had only slight power to elevate the blood pressure and constrict the kidneys (measured by an oncometer), the roots included between these limits were highly effective. Stimulation of the tenth and thirteenth thoracic roots caused especially powerful constriction of the kidneys. Bradford found that the area from which the renal vessels are supplied is extensive and apparently coextensive with that supplying the abdominal vessels. It was thus shown that the splanchnic region is important in the regulation of the arterial pressure and that

² von Bezold, A. Untersuchungen über die Innervation des Herzens, Leipzig, W. Engelmann, 1863.

³ Ludwig, C., and Thiry, L. Ueber den Einfluss des Halsmarkes auf dem Blutstrom, Sitzungsber. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **49** 421, 1864.

⁴ Litten, M. Ueber die Folgen des Verschlusses der Arteria mesaraica superior, Arch. f. path. Anat. **63** 289, 1875.

⁵ Longcope, W. T., and McClintock, A. T. The Effect of Compression of the Superior Mesenteric Artery upon the Systemic Blood Pressure, Univ. Pennsylvania M. Bull. **22** 226, 1909. The Effect of Permanent Constriction of the Splanchnic Arteries and the Association of Cardiac Hypertrophy with Arteriosclerosis, Arch. Int. Med. **6** 439, 1910.

⁶ Bradford, J. Rose. The Innervation of the Renal Blood Vessels, J. Physiol. **10** 358, 1889.

the nervous control of this region lies in the anterior nerve roots issuing from the cord between the third thoracic and the third lumbar segment

The experiments of Burch, Harrison and Blalock⁷ may be taken as indicating the practical importance of this fact. They showed that susceptibility to hemorrhage was only slightly greater in dogs receiving ether than in control unanesthetized animals, but severe circulatory failure and death were produced by the removal of relatively small amounts of blood from animals under spinal anesthesia. The difference was attributed to the fact that the normal dogs and those receiving ether responded to hemorrhage by a compensatory vasoconstriction which tended to maintain the blood pressure, while this constrictor response was diminished or abolished by spinal anesthesia, and therefore a relatively slight decrease in the volume of the blood caused a disproportionately large decline in the pressure.

Cyon and Ludwig⁸ and Bever and Bezold⁹ recognized the importance of the control of the abdominal vessels by the splanchnic nerves. Cutting one of them in curarized or lightly anesthetized rabbits resulted in a fall in pressure of from 30 to 50 mm of mercury, and section of the second one produced a further fall of from 8 to 10 mm of mercury (Cyon and Ludwig). Bever and Bezold observed practically the same lowering of pressure after section of both splanchnic nerves within the thorax as after division of the spinal cord in the cervical region. Stimulation of the distal portion of the severed nerve resulted in marked elevation of the blood pressure, which was lacking when the central end was stimulated (Cyon and Ludwig).

Recovery of the tone of the vessels in normal animals after denervation appears to be a general phenomenon (Grant, Camp, Graybiel and Rothschild¹⁰ and Wilson, Roome and Grimson¹¹). Whether the abnor-

7 Burch, J. C., Harrison, T. R., and Blalock, A. A Comparison of the Effects of Hemorrhage Under Ether Anesthesia and Under Spinal Anesthesia, *Arch Surg* **21** 693 (Oct.) 1930.

8 Cyon, E., and Ludwig, C. Die Reflexe eines der sensiblen Nerven des Herzen auf die motorischen der Blutgefasse, *Arb a d physiol Anstalt zu Leipzig* **1** 128, 1866.

9 Bever, C., and von Bezold, A. Von den Wirkungen der Nervi splanchnici auf den Blutdruck, im Aortensystem, in von Bezold, A. Untersuchungen aus dem physiologischen Laboratorium in Wurzburg, Leipzig, 1867, vol. 1, p. 314.

10 Grant, R. T., Camp, P. D., Graybiel, A., and Rothschild, P. Further Observations on the Vessels and Nerves of the Rabbit's Ear, with Special Reference to the Effects of Denervation, *Clin Sc* **2** 1, 1935.

11 Wilson, H., Roome, N. W., and Grimson, K. Complete Sympathectomy. Observations on Certain Vascular Reactions During and After Complete Exclusion of the Sympathetic Nervous System in Dogs, an Experimental Study, *Ann Surg* **103** 498, 1936.

mal tone in hypertensive animals also is recovered is not known. The tone of the vessels is regained in from thirteen to twenty-five days after section of the splanchnic nerves in cats, and the blood pressure returns to normal (Magnus¹²). The rise in blood pressure which follows stimulation of the splanchnic nerves is believed to depend on two distinct mechanisms: (1) contraction of the peripheral vessels of the splanchnic area due directly to stimulation of the vasoconstrictor nerves supplying that region and (2) contraction of the peripheral vessels throughout the whole organism due to liberation of epinephrine as a result of the direct stimulation of the nerves to the adrenal glands (Anrep¹³ and Lehnendorff¹⁴).

Evidence of a different nature concerning the rôle of the splanchnic region as a regulator of the blood pressure has been furnished by Jansen, Tams and Achelis¹⁵. They found that in dogs closure of the large vessels to the head and extremities resulted in small and transient rises in the arterial pressure. Conversely, closure of the mesenteric artery resulted in marked and sustained rises, thus confirming the findings of Longcope and McClintock⁵. Preliminary closure of the mesenteric artery followed by closure of the vessels to the limbs produced a rise in pressure considerably greater than the sum of the elevations when the procedures were carried out separately. In a normal human being binding three extremities in elastic bandages, the blood pressure being measured in the fourth limb, caused only a temporary rise in the blood pressure, but in a hypertensive patient the rise was greater and prolonged. These observations are taken to mean that in a hypertensive patient the reservoir function of the abdominal vessels has been lost and can no longer compensate for an increase in the volume of blood. These investigators found, further, that cold colonic irrigations, which cause splanchnic vasoconstriction, produced a much greater rise in pressure than cold baths, which cause peripheral vasoconstriction.

That narrowing of the arteries of the extremities does not in itself cause hypertension was noted, among others, by Fishberg¹⁶. He

12 Magnus, R. Ueber peripheren Gefasstonus im Splanchnicusgebiet, *Arch f d ges Physiol* **115** 331, 1906.

13 von Anrep, G. On the Part Played by the Suprarenals in the Normal Vascular Reactions of the Body, *J Physiol* **45** 307, 1912.

14 Lehnendorff, A. Ueber die Ursachen der typischen Schwankungen des allgemeinen Blutdruckes bei Reizung der Vasomotoren, *Arch f Physiol*, 1908, p 362.

15 Jansen, W. H., Tams, W., and Achelis, H. Blutdruckstudien. I. Zur Dynamik des Blutdrucks (nach experimentellen Untersuchungen an Mensch und Tier), *Deutsches Arch f klin Med* **144** 1, 1924.

16 Fishberg, A. M. Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1931, p 193.

observed that the blood pressure was normal in a patient suffering from thrombo-angitis obliterans in whom both legs were amputated and the left arm was severely involved. We have repeatedly noted in this clinic that the arterial pressure is unchanged in a hypertensive patient during attacks characterized by intense pallor of the skin of the fingers (so-called "dead fingers")

Steele and Kirk¹⁷ have presented convincing evidence that the temperature of the skin of a patient with essential hypertension does not differ from that of a normal subject. Diurnal variations in the surface temperature regularly occur in hypertensive patients without any significant change in the arterial pressure. Elevation of the blood pressure evidently does not depend on constriction of the arterioles of the skin, though it may be accompanied with it.

This varied evidence is taken to mean that the splanchnic vessels constitute an important but not the only flexible reservoir which governs the level of the arterial pressure.

It is obvious from clinical observation that constriction of vessels must be present in cases of hypertension in regions other than the splanchnic region. For example, the arterioles in the retina can be seen to be markedly reduced in caliber. Recent important evidence of Prinzmetal and Wilson¹⁸ and Pickering¹⁹ indicated that, so far as conclusions can be drawn from the measurement of the blood flow in the forearm, increased vascular resistance is widespread throughout the body. Since an increase of the blood flow associated with inhibition of the vasoconstrictor impulses to the vessels of the forearm and hand by warming the body was no greater in a patient with hypertension than in a normal subject, it was concluded that the vascular hypertonus was not of vasomotor origin. Prinzmetal and Wilson found that sympathetic vasoconstriction is responsible for the hypertonus of coarctation of the aorta, but with this finding Pickering did not agree.

These results provide evidence that the nervous system plays an unimportant part in the genesis of hypertension. However, clinical observation makes it difficult to believe that it does not play an essential rôle, at least in early stages of certain types of hypertension. The marked fall in the arterial pressure of a hypertensive patient caused by spinal anesthesia is not readily explained without recourse to the

17 Steele, J. M., and Kirk, E. The Significance of the Vessels of the Skin in Essential Hypertension, *J. Clin. Investigation* **13** 895, 1934.

18 Prinzmetal, M., and Wilson, C. The Nature of the Peripheral Resistance in Arterial Hypertension with Special Reference to the Vasomotor System, *J. Clin. Investigation* **15** 63, 1936.

19 Pickering, G. W. The Peripheral Resistance in Persistent Arterial Hypertension, *Clin. Sc.* **2** 209, 1936.

vasomotor system Possibly during the early stages of essential hypertension heightened vasoconstriction arises from morbid activity of the nervous system but as the disease progresses a local fault of the vessel wall provides for continuance of the disease

Since alterations of the physiologic state of varied sorts, such as pregnancy, nephritis, pituitary basophilism, constriction of the renal arteries and emotion, often are exhibited by the one sign they have in common, namely, hypertension, the possibility may be entertained that a common substance is liberated which is not directly pressor in action but which acts on the vessel walls to induce hypertonus

Though the mechanism causing hypertension is not known, it is of importance to ascertain what, if any, influence the nervous system has in its genesis The operation of Adson and Brown²⁰ provides such an opportunity

OPERATION

Section of the anterior roots as we have performed it consists in the bilateral division of the anterior roots of the sixth dorsal to the second lumbar spinal nerve The positive identification before operation of the spinous process of the first lumbar vertebra and its relation to the overlying skin has been helpful in determining the lower limit of the incision The identification of the last digitation of the dentate ligament after the dura has been opened has aided in determining the roots to be divided, for it is attached to the dura between the twelfth dorsal and the first lumbar nerve (fig 1)

With the patient under general anesthesia the laminae of the first lumbar to and including the sixth dorsal vertebra are removed in order to expose as widely as possible the dura mater covering the cord Hemorrhage is meticulously controlled before the dura is opened The incision in the dura is made in the midline and carried to either extremity of the bony defect The edges of the incised dura are held apart with a series of fine silk threads, as shown in the accompanying illustration A rent is made in the pia-arachnoid, and the cerebrospinal fluid is removed by suction

After the nerves under consideration have been identified the operation of dividing the anterior roots is begun either at the upper or the lower portion of the exposed cord A fine clamp is placed on the digitation of the dentate ligament close to the dura, and its attachment to the dura is separated with a knife By drawing the clamp inward or mesially one can slightly rotate the spinal cord on its long axis, the

20 Adson, A W, and Brown, G E Malignant Hypertension Report of Case Treated by Bilateral Section of Anterior Spinal Nerve Roots from the Sixth Thoracic to the Second Lumbar, Inclusive, J A M A 102 1115 (April 7) 1934

maneuver bringing into view the anterior root of the spinal nerve. It is closely applied to the lateral or ventrolateral aspect of the cord and is covered by the pia-arachnoid. It can be readily traced downward and outward to join the posterior root. After the nerve has been identified

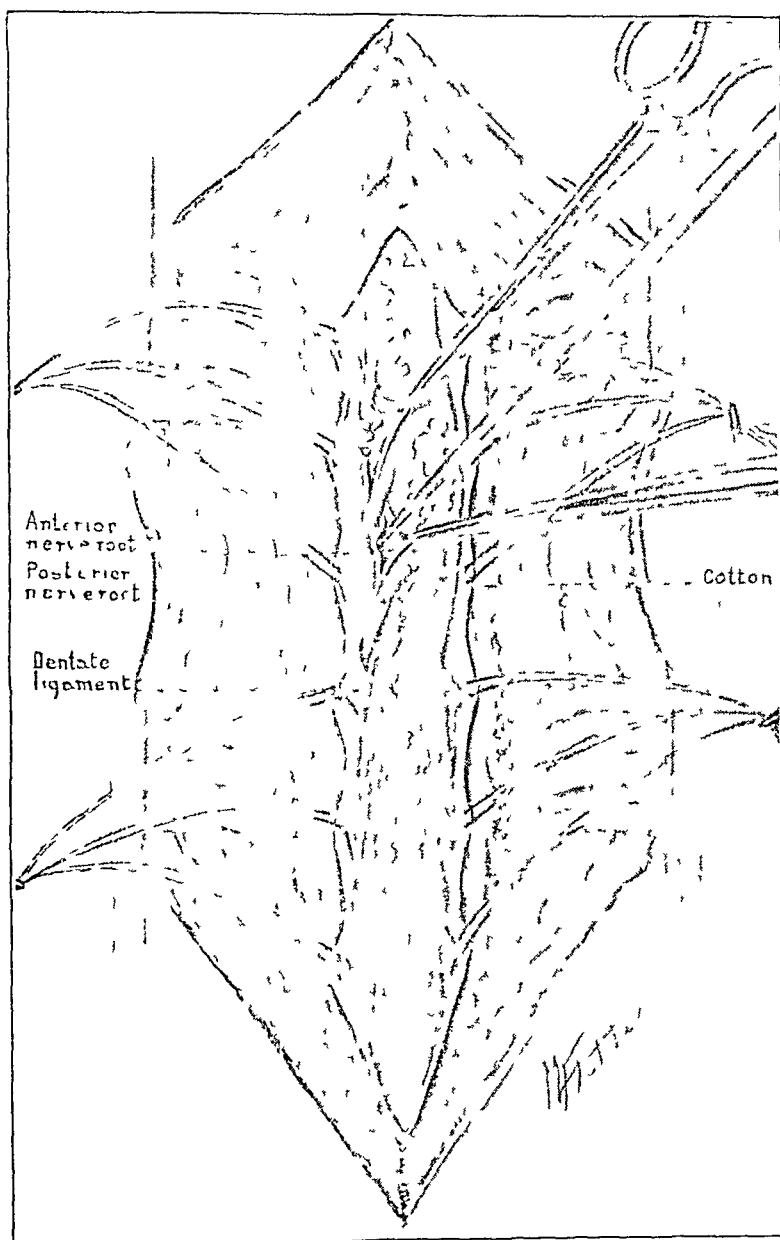


Fig 1—Drawing showing the operative field in section of the anterior roots from the sixth dorsal to the second lumbar spinal nerve

a rent is made in the pia-arachnoid covering it, and the nerve is raised from the cord with a blunt right angle nerve hook. It is doubly ligated with fine silk and divided between the ligatures. The ligation of the nerve is deemed important because of the blood vessels which accompany

it and which in many instances cannot satisfactorily be separated from it. In other cases the accompanying blood vessels are of sufficient size so that they may be separated from the nerve and preserved. Their preservation is desirable, for they contribute to the nourishment of the cord.

In this fashion each pair of anterior spinal nerves is divided, and during the procedure frequent observations of the blood pressure are made by the anesthetist to determine the effect produced. When division of the nerves has been completed, the dura is closed with interrupted fine silk sutures. The muscles, fascia and skin also are closed with interrupted silk sutures.

While from anatomic and physiologic considerations the division of the sixth dorsal to the second lumbar anterior root is probably desirable, we have, as a matter of practice, in only two instances divided all these nerves. In the remaining cases we have omitted division of the sixth dorsal and sometimes of the seventh and eighth dorsal nerves and frequently have omitted division of the second lumbar nerve. Two considerations chiefly have led us to vary the procedure. We have been anxious to determine whether early in cases of essential hypertension the division of the ninth, tenth, eleventh and twelfth dorsal and first lumbar nerves is sufficient to lower the blood pressure significantly, for physiologic experiments indicate that the tenth, eleventh and twelfth dorsal and first lumbar nerves are importantly concerned in controlling the blood pressure. Our observations, still insufficient in number, suggest that in cases of advanced involvement the division of all the nerves mentioned should be undertaken, in patients with an early stage of hypertension division of the ninth dorsal to the first lumbar nerve, inclusive, has thus far sufficed. Again, and especially in early stages, the rapid and sometimes rather alarming fall in blood pressure during the operation has made us hesitate to divide the entire group of nerves. The variation in the reaction of patients on the operating table has led us to divide first the ninth dorsal to the first lumbar nerve, inclusive, and to be guided as regards the division of the others by the patient's reaction. As our experience has increased we have become less fearful of a fall in blood pressure during the operation.

Aside from this fall in blood pressure there is little that occurs during the operative procedure to warrant comment. The preservation of a clear field by the prevention of hemorrhage is the most important point in the performance of section of the roots. In our experience hemorrhage is most likely to occur from the small vessels accompanying the nerve roots and by manipulations too near the point at which the roots perforate the dura. Postoperatively, aside from the low blood pressure,

which we have combated chiefly by intravenous injections of dextrose solution, there have thus far been few serious complications. Difficulty in evacuating the bladder and bowel for forty-eight hours after operation has been fairly frequent and is attributed to the loss of function of the abdominal muscles. In one case the inability to control the bladder persisted for seven weeks after the operation.

In our later experience the operation has been divided into two stages, the first terminating with the completion of the laminectomy and the complete exposure of the dura, the second consisting in the opening of the dura and the division of the anterior nerve roots. An interval of several days to a week was allowed to elapse between stages.

PLAN OF STUDY

Care of the Patient—Measurements of the blood pressure were made at 9:30 a. m. daily with the patient in bed. During the period of observation before operation, which extended for a month or more, the patient was not allowed out of bed for any purpose. It should be emphasized that *each dot on the graphs under the heading blood pressure usually represents from three to five measurements which were averaged for convenience in charting*. After operation the patient was allowed up at will, but measurements of the blood pressure were made with the patient in bed, hence the measurements cannot be considered strictly comparable with those made before operation. Sedatives, including chloral hydrate, amytal and less often sodium bromide, were employed liberally before but not after operation. The diet was unrestricted as to quality or amount. Electrocardiographic records were made before and after operation by Dr. Alfred Cohn and Miss M. Alleman.

Clinical Observations—Renal efficiency was measured by the urea clearance test and the ability of the kidneys to concentrate urine. The urea clearance test was employed not only because it is a most delicate test but because Van Slyke, Rhoads, Hiller and Alving²¹ have shown that in dogs it parallels the renal blood flow. The specific gravity was measured for a twelve hour specimen voided at the end of twenty-four hours without fluids. If protein was present in sufficient amount to contribute to the specific gravity, a correction was made for it, that is, 0.003 was subtracted from the total specific gravity for each 1 per cent of protein.²² The number of formed elements in the urine was estimated by the technic of Addis.²³ Not more than 500,000 red blood cells are excreted by a person with normal kidneys. The protein content of the urine was measured by the method of Shevky and Stafford, as slightly modified by MacKay.²⁴ The protein content

21 Van Slyke, D. D., Rhoads, C. P., Hiller, A., and Alving, A. The Relationship of the Urea Clearance to the Renal Blood Flow, *Am. J. Physiol.* **110**: 387, 1934.

22 Lashmet, F. H., and Newburgh, L. H. An Improved Concentration Test of Renal Function, *J. A. M. A.* **99**: 1396 (Oct. 22) 1932.

23 Addis, T. The Number of Formed Elements in the Urinary Sediment of Normal Individuals, *J. Clin. Investigation* **2**: 409, 1926.

24 MacKay, cited by Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 682.

of the plasma was ascertained by the method of Howe,²⁵ and the hemoglobin content was measured by the Van Slyke and Neill²⁶ method

Explanation of the Charts—On the charts the mean normal of each measurement represented is drawn as a base line, the shaded areas between the base line and the points representing observations indicate the degree of deviation above or below the average normal. The brackets at the left of the scales for urea clearance, concentration of urine and hematuria indicate the range of normal variability. The normal base line for the hemoglobin value varies with the patient's age and sex. As previously stated, measurements of the blood pressure were made daily at 9 30 a m *but are represented in the charts as averages*. The black areas representing edema, according to the height of the black area in quarters of the total space, indicate (1) a trace, (2) moderate pitting, (3) marked pitting and (4) general edema with ascites. Morbid changes in the eyegrounds are recorded as follows: (1) constriction of the arterioles, (2) arteriosclerosis, (3) exudate, (4) hemorrhages and (5) papilledema. The estimated time which elapsed between the onset of the disease and the patient's admission to the hospital is recorded on the lowest line of the chart as the first number following the word months. The other numbers in the bottom row indicate months after the patient's first admission to the hospital.

Selection of Patients—It is possible though not proved that the patient who exhibits marked flexibility in the vascular system will obtain the greatest benefit from section of the anterior roots. The criteria for vascular flexibility which have been employed are of several kinds. The first is a fall in blood pressure when the patient is put to bed. The second is a fall in the blood pressure when colloidal sulfur or acetylbetamethylcholine is injected intramuscularly, when sodium thiocyanate is given by mouth or when amyl nitrite is inhaled. The third is the daily fluctuation in the blood pressure level.

While previous cardiac decompensation and the presence of a markedly enlarged heart, along with changes indicative of myocardial damage as indicated by the electrocardiogram, are not desirable when the operation is elective, it has not been our experience that these interdict it. One case (11), in particular, illustrates this view. Although the heart was greatly enlarged and the T wave was negative in leads I and II, with preponderance of the left ventricle, the patient bore a two stage operation without difficulty.

Extensive changes in the fundi also were considered indicative of a rapidly advancing morbid process, but they did not contraindicate operation. Since the fall in blood pressure has not appeared to reduce the renal efficiency, as measured by the urea clearance test or the ability to concentrate urine, moderate degrees of renal insufficiency (above 30 per cent of the normal urea clearance) may not jeopardize the life of the patient.

We have not considered it justifiable to select only those patients in whom, in our opinion, a maximum fall in blood pressure might occur. Some have been operated on in the terminal stage of the disease and some who have shown little evidence of vascular flexibility have been operated on in the hope that the blood pressure might be reduced, contrary to our prognosis.

25 Howe P E. The Determination of Proteins in the Blood—a Micro Method, *J Biol Chem* **49** 109, 1921.

26 Van Slyke D D, and Neill, J M. The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J Biol Chem* **61** 573, 1924.

REPORT OF CASES

CASE 1—The history of this patient has been reported previously²⁷ We wish to add to this record that it is now thirty-seven months since the operation was

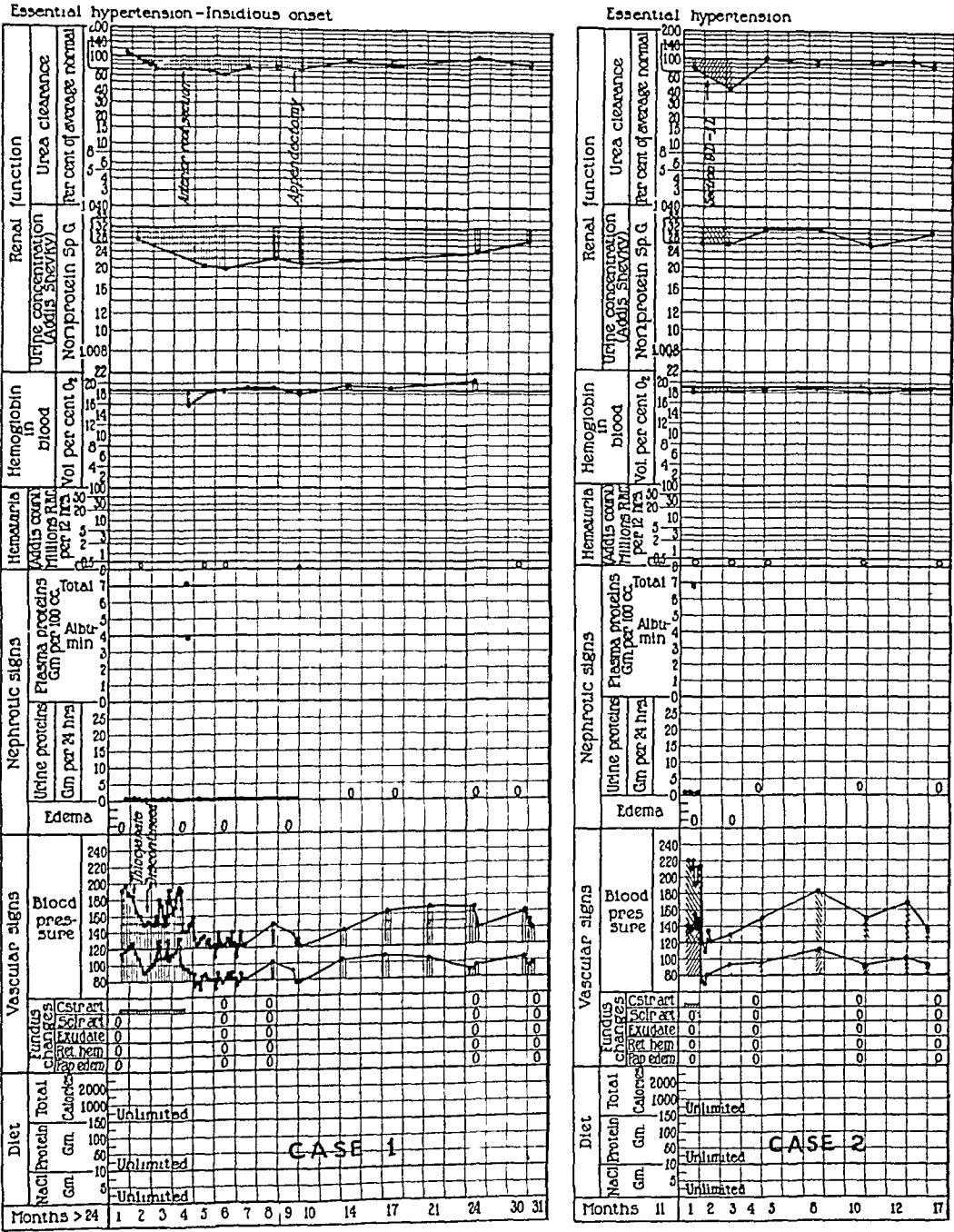


Fig 2—Case 1 was that of a woman aged 23 with essential hypertension of insidious onset. She was 157 cm tall, and her ideal weight was 57 Kg. Case 2 was that of a woman aged 24 with essential hypertension. She was 165.5 cm tall, and her ideal weight was 61.5 Kg.

²⁷ Page, I. H., and Heuer, G. J. A Surgical Treatment of Essential Hypertension, *J Clin Investigation* 14:22, 1935.

performed. The symptoms have not returned, and the patient has resumed her work in an office. The blood pressure level after one-half hour's rest in bed varies from 140 systolic and 106 diastolic to 162 systolic and 110 diastolic. The renal function has remained normal, and there has been no change in the size of the cardiac shadow, as measured on an x-ray plate. Since considerably more data on this patient are now available, the graphic chart is again presented. Dr E V Allen concurred with us as to the advisability of operation in this case.

CASE 2—A 24 year old housewife, referred to us by Dr M C Rosenkranz, complained of dizziness, nausea, weakness, nervousness and ringing in the ears. Her father died of hypertension at 44 years of age. One sister 32 years old has had hypertension for five years. Four years ago this patient noticed that she had attacks during which her face and the upper part of the chest became spontaneously blotchy red, she had spots before her eyes and some dizziness. The arterial pressure was found to be 130 mm. For the past year she had been distressed by nervousness, emotional instability, ringing in the ears, nausea, insomnia, weakness and dizziness. Eight months previous to her admission to the hospital the arterial pressure was 180 mm, and four months later it was 220 mm. Recently there was a slight loss of memory.

The patient was of masculine build, and there was a somewhat masculine distribution of hair. The beard was almost masculine. The disks of the fundi were sharply outlined and slightly hyperemic. There was slight sausage-shaped constriction in some of the arterioles, and the veins were moderately dilated. There was no perivascularitis, hemorrhage or exudate. The thyroid gland was slightly and diffusely enlarged, but there were none of the classic signs of exophthalmic goiter. The size of the heart was normal, as measured by percussion, and it was not overactive. The aortic second sound was clearly accentuated. Measurements from an x-ray plate showed a total transverse diameter of 10.5 cm and an internal diameter of the chest of 22 cm. The peripheral vessels were a little thickened but not tortuous. The coloring of the skin of the extremities was unusual, being mottled deep pink and bluish. Both the hands and the feet were cold and covered with perspiration. Both superficial and deep reflexes were equal on the two sides and moderately active.

The basal metabolic rate was +15 per cent. The electrocardiographic record showed that the T wave was positive in leads I and II and negative in lead III. The conduction time was 0.15 second. There was preponderance of the left ventricle, and the rhythm was normal. Roentgenograms of the skull showed it to be normal. The Kline test was negative.

The blood pressure when the patient had been at rest in bed for nineteen days varied from 180 systolic and 130 diastolic to 220 systolic and 160 diastolic, the average level being 206 systolic and 148 diastolic.

Section of the anterior roots from the ninth thoracic to the first lumbar segment on the left side and from the ninth to the twelfth thoracic segment on the right side was performed on Nov 2, 1934. During the operation the arterial pressure fell from 195 systolic and 140 diastolic to 120 systolic and 70 diastolic.

The postoperative course was uneventful. The blood pressure averaged from 130 to 148 systolic and from 90 to 96 diastolic for the first four months. The improvement in the subjective symptoms was remarkable. The patient has returned to work.

Comment—This patient had hypertension which appeared to be rapidly advancing. The disease was found in other members of her family. Four years prior to her admission to the hospital the arterial

pressure was normal, but eight months before her admission to the hospital it was 180 mm and four months later 220 mm. She suffered from many subjective symptoms. The "hypertensive diencephalic syndrome" was especially marked. Rest in bed and sedatives did not reduce the pressure significantly. Five anterior roots were severed on one side and four on the other (ninth thoracic to first lumbar segment). The arterial pressure fell from an average level of 206 systolic and 148 diastolic to 140 systolic and 94 diastolic and remained there for about five months. Since then (in fifteen months) it has risen to 170 systolic and 110 diastolic. The subjective symptoms, excepting those included in the "diencephalic syndrome," disappeared, and the patient now works from 9 in the morning to 6 at night in a store.

CASE 3—A 17 year old girl had complained of headaches and dizziness for three years. There was no history of vascular disease in the family. For the past few years she had noticed that she blushed extremely easily and simultaneously had palpitations, sweating and slight shortness of breath. She had had dull pains over the precordium.

One year before her admission to the hospital she decided to withdraw from the world and become a nun. The arterial pressure was found to be 150 systolic and 102 diastolic. Her emotional make-up was highly unstable, and she suffered from many conflicts. She was referred to Dr. S. Clinton Levine, who found that the pressure was 174 systolic and 124 diastolic. Six months later she was admitted to the hospital.

Physical examination showed that the girl was well proportioned. She did not appear ill. She blushed violently, the blush extending down over the upper part of the chest, and over the same area were small beads of perspiration. The hands and feet were cold. The distribution of hair was normal. The nerve heads of the eyegrounds were slightly hyperemic, but no papilledema was present. The arterioles were tortuous (grade 2), but there was almost no perivascularitis. The veins were slightly dilated. There was no hemorrhage or exudate. The thyroid gland was slightly and diffusely enlarged. The heart was overactive, and the rate was 88. It was not enlarged. Measurements made from an x-ray plate showed a total transverse diameter of 10.2 cm, and the internal diameter of the chest was 23.5 cm. The heart was pear shaped and the aorta normal. The aortic and pulmonary second sounds were not accentuated. The peripheral vessels were not thickened. Both superficial and deep reflexes were active and equal on the two sides. None of the classic symptoms of exophthalmic goiter were present except slight enlargement of the gland.

The electrocardiogram showed a positive T wave in leads I and II and a negative T wave in lead III, a PR interval of 0.16 second, preponderance of the left ventricle and normal rhythm. The basal metabolism varied from -11 to +8 on a number of occasions. The blood sugar value was 103 mg per hundred cubic centimeters. The sella turcica was small, but the floor was clearly defined. The Kline and Wassermann tests were negative. The blood pressure during the preliminary examinations in the outpatient clinic varied from 190 systolic and 136 diastolic to 210 systolic and 144 diastolic. When the patient was admitted to the hospital it quickly fell to an average of 180 systolic and 122 diastolic, falling as low as 136 systolic and 94 diastolic at one reading. After the patient

had been in the hospital for five weeks the pressure was still elevated, the diastolic pressure, in particular, reaching 130 mm or more

On Dec 18, 1934, the anterior nerve roots from the ninth thoracic to the first lumbar segment, inclusive, were severed. The postoperative course was

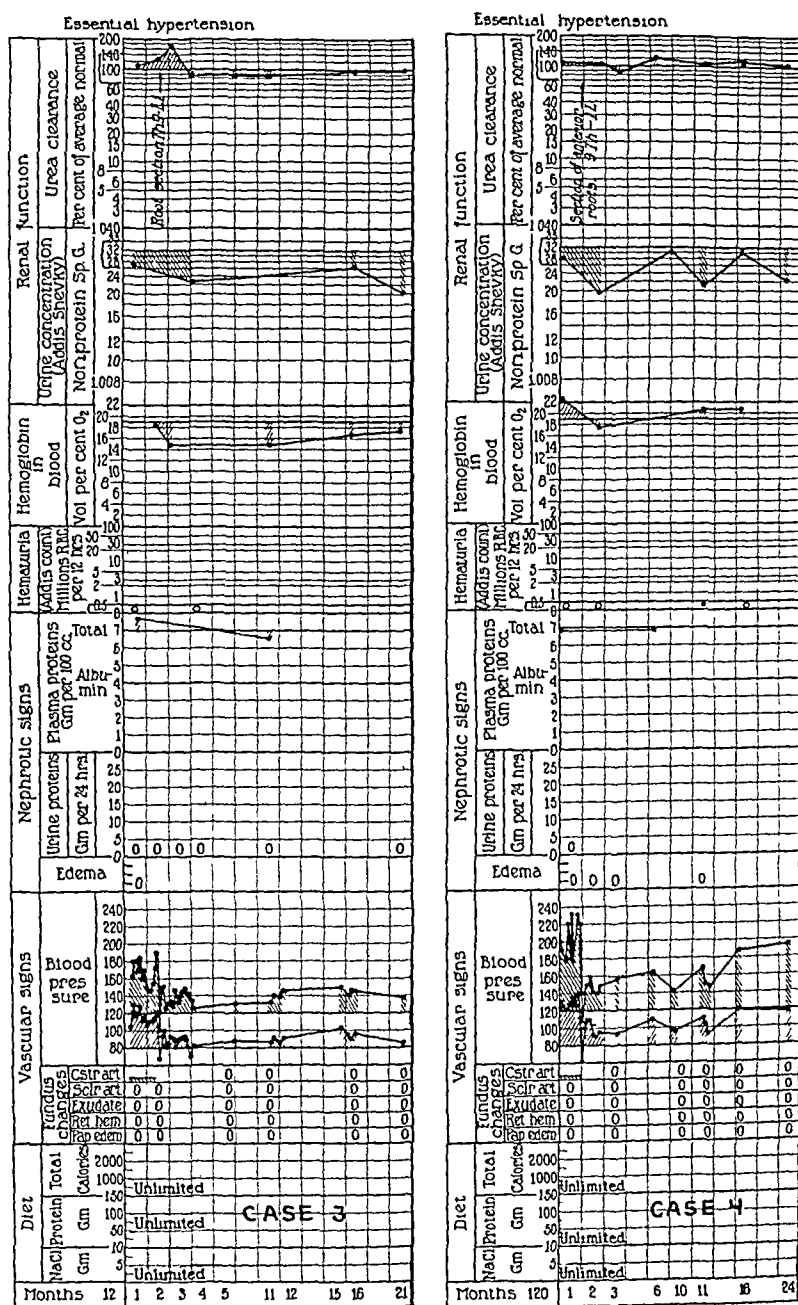


Fig 3—Case 3 was that of a girl aged 17 years with essential hypertension. She was 160.5 cm tall, and her ideal weight was 58.3 Kg. Case 4 was that of a woman aged 32 with essential hypertension. She was 158.5 cm tall, and her ideal weight was 50.8 Kg.

uneventful. Distention was easily controlled by pitressin and enemas. The patient was allowed up on the fourteenth postoperative day. The arterial pressure

fell to 100 systolic and 70 diastolic on the day of operation. During the next weeks it averaged 130 systolic and 84 diastolic. Reduced iron was administered to aid in overcoming a slight degree of anemia which had developed. There was little change in the fundi of the eyes. Twenty-six months after operation the patient appeared to be in good health. Excitement caused the arterial pressure to rise to 162 systolic and 106 diastolic, but the level after rest was 138 systolic and 90 diastolic. The attacks suggestive of the "diencephalic syndrome" were somewhat less severe than before operation. All other symptoms had disappeared.

Comment—This was a case of marked hypertension in a young girl. Symptoms and signs of the "hypertensive diencephalic syndrome" were prominent. Five pairs of anterior nerve roots were sectioned (ninth thoracic to first lumbar). The blood pressure fell from an average preoperative level of 180 systolic and 122 diastolic to 138 systolic and 90 diastolic and has remained at this level for twenty-six months. Except for the "diencephalic syndrome," all subjective symptoms disappeared. The operation was considered successful.

CASE 4—A 32 year old woman, referred to us by Dr. H. Meyersburg, had noticed shortness of breath which was unrelated to physical exertion twelve years before her admission to the hospital. At that time she was emotionally upset, and one year later suffered a "nervous breakdown." She was married the following year. Two years later a dead fetus was delivered. The physician told her that she had hypertension and excreted a small amount of albumin. Her emotional instability increased and two years later she was divorced. Since then emotional instability and a feeling of pressure in the head and abdomen have been the outstanding symptoms. For the past ten years she had been greatly embarrassed by spontaneous blushing, which caused the skin of her face and the upper part of the chest to become mottled red and white. Her mother and sister also exhibited this phenomenon, and the sister, in addition, suffered from hypertension.

The patient was a well developed woman, obviously high strung and nervous. The distribution of hair was normal. Examination of the fundi showed that the nerve heads, arterioles and veins were normal. No perivasculitis, exudate or hemorrhages were noted. The heart was not enlarged, as measured by percussion. X-ray measurements showed a total transverse diameter of 10.6 cm. and an internal diameter of the chest of 23.6 cm. The rate, rhythm and sounds were normal. The peripheral vessels were not thickened or tortuous.

The electrocardiogram showed an upright T wave in leads I and II and a negative T wave in lead III, sinus tachycardia, a conduction time of 0.16 second and a normal rhythm. The basal metabolic rate was (first test) -12 per cent and (second test) -7 per cent. Three days later it was (first test) $+32$ per cent and (second test) $+11$ per cent. The Wassermann test was negative. The arterial pressure varied from 176 systolic and 126 diastolic to 230 systolic and 145 diastolic during the first twenty days the patient was in bed. The average pressure was 210 systolic and 130 diastolic. While the blood pressure was relatively fixed at an elevated level, particularly the diastolic pressure, the cardiac and renal functions were good.

On Nov. 30, 1934, the anterior roots from the ninth thoracic to the first lumbar segment were cut. During the operation the arterial pressure fell from 190 systolic and 130 diastolic to 110 systolic and 70 diastolic. The postoperative

course was uneventful, and fourteen days later the patient was allowed to walk. The blood pressure fell to an average level of 160 systolic and 104 diastolic, but after twenty-two months it was 190 systolic and 118 diastolic. The "diencephalic syndrome" continued unaltered, but the sensation of pressure in the head and abdomen disappeared. The abdomen protruded slightly but not sufficiently to require a binder. The superficial abdominal reflexes were absent, and there was no change in cutaneous sensibility. Emotional excitement caused the arterial pressure to rise to 200 systolic and 130 diastolic. Measurements of the heart from x-ray plates taken eleven months after the operation showed no change from the preoperative size.

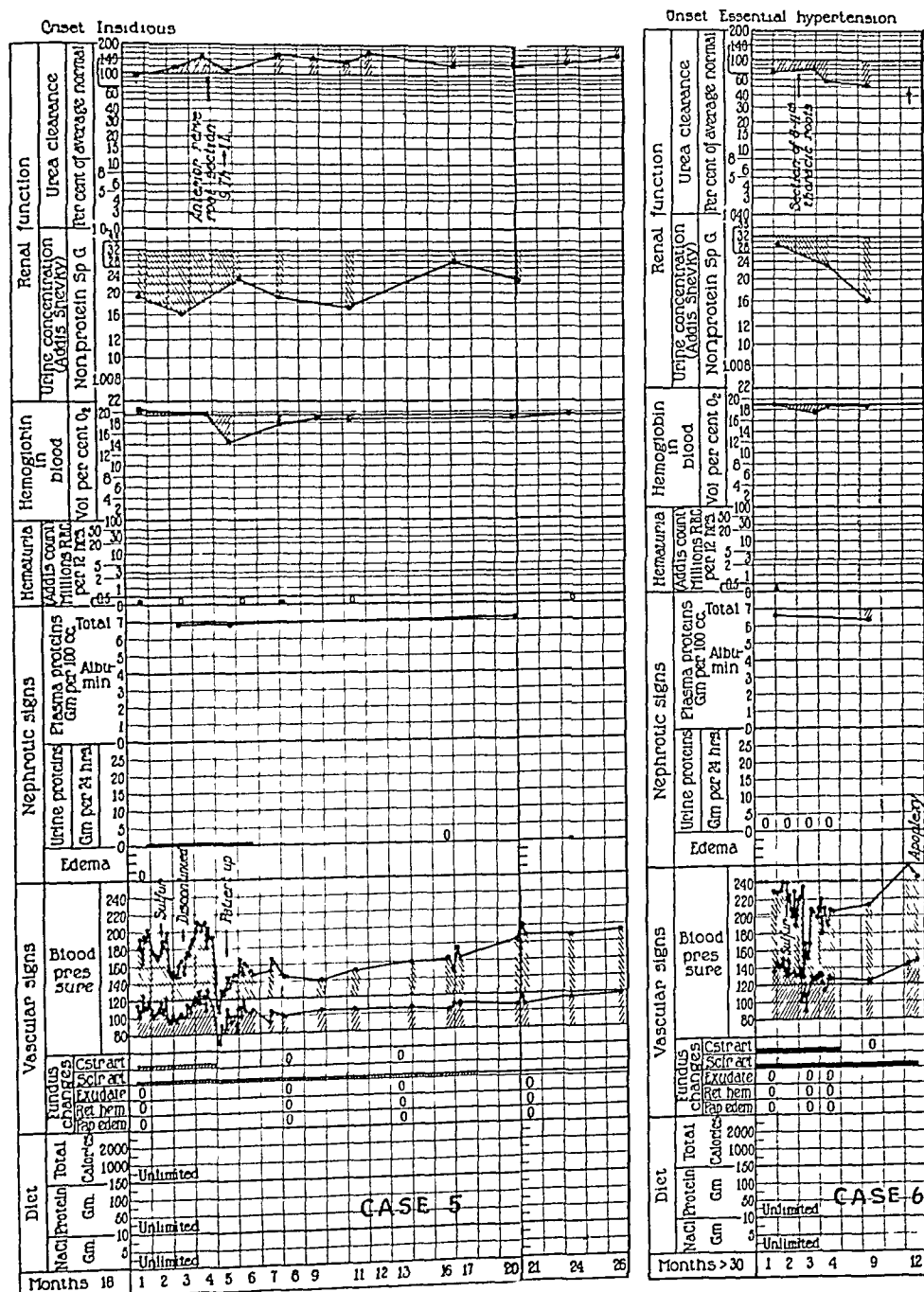
Comment—Section of five pairs of anterior roots (ninth thoracic to first lumbar) clearly reduced the blood pressure in this case. Associated with the reduction in arterial pressure was the disappearance of the sensation of pressure in the head and abdomen but no change in the intensity or the frequency of the attacks characterized as the "hypertensive diencephalic syndrome." After eleven months it appeared that emotional instability was still present. Twenty-seven months after operation the arterial pressure had risen to a level somewhat below the preoperative level. The patient felt much improved but the blood pressure had not been permanently reduced.

CASE 5—A 25 year old housewife, referred to us by Dr. Mary Halton, complained chiefly of daily headaches for the past year and one-half. Hypertension had not occurred in her family. She said she thought she was more than normally excitable. Six years before her admission to the hospital the blood pressure was found to be 95 systolic and 60 diastolic. Three years before her admission to the hospital the arterial pressure was again measured because of insomnia and nervousness and was found to be 142 systolic and 90 diastolic, one year before admission it was 150 systolic and 95 diastolic, five months before admission it was 170 systolic and 100 diastolic, and on admission it was 182 systolic and 116 diastolic. Loss of appetite, restlessness, fatigability, dizziness, faintness and severe headaches were the outstanding symptoms. She also had attacks characterized by flushing of the face, involuntary crying and palpitation. Shortness of breath on exertion was noticed a few months before admission. She noticed that the hair on her body has grown rapidly in the past two years. Nocturia occurred (six or eight times a night).

The patient was a well developed woman. The coarse, abundant hair showed a masculine type of distribution. She appeared nervous and perspired freely. The disks of the fundi were normal, and the arterioles in some places showed slight tortuosity and sausage-like constriction. There was almost no perivascularitis. Hemorrhages or exudates were not seen. The tonsils had been removed. The thyroid gland was not palpable. The heart was of normal size, as measured by percussion. Roentgenograms showed a maximum diameter of 7.5 cm. on the left and 4.5 cm. on the right, a total transverse diameter of 12 cm. and an internal diameter of the chest of 25 cm. The sounds were of good quality, and the aortic and pulmonic second sounds were not accentuated. The pulse rate was 104. The peripheral vessels were not thickened. There was no tremor in the outstretched fingers. Both superficial and deep reflexes were equal in strength on the two sides but hyperactive. The electrocardiographic record showed

T waves positive in all leads, a conduction time of 0.14 second, a diphasic P wave in lead III and preponderance of the left ventricle. The sella turcica appeared normal in an x-ray plate.

During the first twenty-seven days that the patient was in bed without treatment other than sedatives, the arterial pressure varied from 148 to 264 systolic



and from 90 to 148 diastolic, averaging about 184 systolic and 116 diastolic. Colloidal sulfur, 1 cc twice daily, reduced the arterial pressure to an average level of 152 systolic and 100 diastolic, but even under this treatment it slowly rose to 170 systolic and 100 diastolic. When this treatment was discontinued it rose to 210 systolic and 116 diastolic. After fourteen weeks of rest in bed the pressure had risen from 182 systolic and 116 diastolic to 200 systolic and 122 diastolic. The patient complained regularly of severe headaches, fleeting pains throughout the body and tightness over the scalp.

On Oct 29, 1934, laminectomy was performed from the sixth thoracic to the second lumbar segment. Because the blood pressure varied precariously, the operation was done in two stages. Two days later the wound was reopened and the anterior nerve roots were severed from the sixth thoracic to the second lumbar segment, inclusive. The course was uneventful except for considerable distention. An intravenous pyelogram showed that no pathologic changes had occurred in the renal pelvis. During convalescence the arterial pressure varied considerably and after four weeks averaged 146 systolic and 106 diastolic. Four months after operation it was 140 systolic and 100 diastolic and seven months later 152 systolic and 106 diastolic. The subjective symptoms disappeared completely. Constriction in the arterioles of the retina was no longer observed.

Comment—This was a case of severe hypertension in a young woman of more than a year's duration with marked subjective symptoms. Anatomic changes in the vascular system were not evident. Nine pairs of anterior roots were severed (sixth thoracic to second lumbar). An average fall in pressure of 38 mm systolic and 10 mm diastolic occurred, and the wide swings in pressure (up to 264 systolic and 148 diastolic) disappeared. The subjective symptoms were no longer present, except for occasional headaches.

CASE 6—A 40 year old woman, referred to us by Dr Walter Niles, complained of headaches and a change of disposition for sixteen months. She led a busy life as a supervisor of stenographers. Sixteen months before admission to the hospital she noticed that she was becoming exceedingly nervous and irritable and that she tired easily. A dull continuous pain was felt over the precordium, and exertion caused palpitations and dyspnea. Eight months before her admission to the hospital swelling of the ankles occurred in the evening. Pressure and a feeling of constriction over the vertex became annoying symptoms along with repeated severe headaches. The menstrual periods were regular, and the flow was more profuse than usual. There was a marked decrease in libido. Three months before her admission the left arm became numb, white and cold up to the elbow. This attack lasted for about ten days and disappeared without residual paralysis. The blood pressure was 210 mm systolic one year before admission and 230 mm systolic three months before admission. In the past month headaches and fatigue had been so severe as to confine the patient to her room.

Examination disclosed that the patient was a well developed, slightly overweight woman. The disks of the fundi were normal, but the arterioles were constricted (grade 2) and tortuous (grade 2), especially in the macular field. There was practically no perivasculitis. The veins were dilated (grade 3) and tortuous, and arteriovenous compression was observed. There was no hemorrhage or exudate. The thyroid gland was not palpable. The heart beat had a moderate thrust and was increased in rate above normal. The measurements from an x-ray plate

showed a total transverse diameter of 14.8 cm and an internal diameter of the chest of 26 cm. The aorta was tortuous and more radio-opaque than normal. The sounds were of good quality, but the aortic second sound was markedly accentuated and the pulmonic second sound less so. The peripheral vessels were slightly thickened. The abdominal wall was relaxed and flabby. Roentgen examination of the skull showed that the sella turcica was normal.

The electrocardiogram showed positive T waves in leads I and II and a negative T wave in lead III, a conduction time of 0.16 second, preponderance of the left ventricle and a normal rhythm. The Wassermann reaction was negative. The basal metabolic rate was +1. The arterial blood pressure varied from 208 to 260 mm systolic and from 132 to 160 mm diastolic, averaging 230 systolic and 142 diastolic during fourteen days of rest in bed. Intramuscular injections of colloidal sulfur reduced the pressure to a minimum of 180 systolic and 122 diastolic within fifteen days.

On March 7, 1935, laminectomy was performed, and the anterior roots were severed from the ninth to and including the twelfth. Marked calcific arachnoiditis was found, which increased the difficulties of the operation greatly. The post-operative course was uneventful. The arterial pressure varied from 180 to 220 mm systolic and from 110 to 138 mm diastolic, averaging 210 systolic and 122 diastolic, with the patient up and about the ward during the next month and a half. The electrocardiogram was unchanged. After the operation the subjective symptoms disappeared. The absence of headaches was striking. The patient died of apoplexy nine months after operation.

Comment—This patient suffered from marked generalized arteriosclerosis as well as hypertension. The arterial pressure was fixed at a high level and showed little flexibility. Dr. Niles agreed with us that because of the severe subjective symptoms and the hopeless outlook operation should be attempted. Because of the difficulty of operating on a spinal cord covered with arachnoidal calcified plaques, only four pairs of dorsal roots were cut. The fall in arterial pressure averaged 20 mm systolic and 20 mm diastolic and was associated with a disappearance of the subjective symptoms. Death occurred from apoplexy nine months after operation.

CASE 7—A 35 year old housewife complained of headaches, precordial pain, dizzy spells, easy fatigability and dyspnea on exertion for three years. There was no history of vascular disease in the family. Three years before her admission to the hospital hypertension was discovered by her physician, Dr. J. Auslander. Since then, severe headaches lasting for days has been the most characteristic symptom. There has been no change in the menses or libido.

Examination showed that the patient was well developed and did not appear ill. Corneal opacities were present in both eyes, and the pupils reacted to light and in accommodation actively. The arterioles of the fundi were slightly constricted and tortuous, and the disks were normal. There was no hemorrhage or exudate. The thyroid gland was moderately and diffusely enlarged without bruit. No other signs of exophthalmic goiter were found. The heart was not enlarged. Measurements from an x-ray plate showed a maximum diameter of 8.9 cm to the left and 2.9 cm to the right, a total transverse diameter of 11.8 cm and an internal diameter of the chest of 25 cm. The aorta was dilated and prominent. The

a normal rhythm. The basal metabolic rate was +7 per cent. When the patient was admitted to the hospital the arterial pressure was 212 systolic and 126 diastolic and varied from 182 to 212 mm systolic and 108 to 132 mm diastolic during fourteen days of rest in bed. The average pressure was 190 systolic and 122 diastolic.

On Jan 25, 1935, the anterior nerve roots from the seventh to the twelfth thoracic segment were severed. The arterial pressure fell to 90 systolic and 60 diastolic immediately after the operation. There was difficulty in voiding after the operation, and frequent catheterization was necessary. The patient sat up on the ninth day. Gastric analysis was performed before and seventeen days after operation. No marked difference was found in either free or total acid in the specimen taken during fasting or that obtained after the injection of 0.5 mg of histamine.

The arterial pressure varied from 160 to 184 mm systolic and from 98 to 122 mm diastolic during thirty-nine days of convalescence. The average was 176 systolic and 114 diastolic. This level was not strictly comparable with the pre-operative level, because it was measured with the patient up and about the ward instead of in bed. Four months after operation the arterial pressure at a single examination was 200 systolic and 120 diastolic. There was no apparent postoperative change in the size of the cardiac shadow, and there were no changes in the eyegrounds.

Comment—This was a case of essential hypertension of long duration but relatively benign. Subjective symptoms were marked before operation. Six pairs of anterior roots (seventh to twelfth thoracic) were cut. While almost complete symptomatic relief was obtained, the arterial pressure during the first four months fell on an average of only 14 mm systolic and 10 mm diastolic. It is our present opinion that the course of the disease was not significantly altered.

CASE 8—A 25 year old nurse, referred to us by Dr. C. Boettiger, of Flushing, Long Island, complained of headaches, nausea and dizziness for two years. She stated that she had rheumatic fever with swollen joints at the age of 7 years. Seven years before admission to the hospital she had an appendectomy performed, after which pneumonia developed. Two years before her admission to the hospital a physician told her that she had rheumatic heart disease. She had always been nervous and high strung. For the past few years she noticed that she perspired freely and that her hands and feet were usually cold and moist. Flushing of the skin of the face and the upper part of the chest, palpitations, crying without apparent reason and consciousness of increased intestinal movements became annoying symptoms. Two years before admission a life insurance policy was granted, although her blood pressure was 140 mm systolic. In the past year excruciating headaches which often lasted for two days occurred, usually associated with nausea, dizziness and a feeling of constriction of the scalp. After a day's work she often had marked edema of the ankles, which disappeared after rest. She smoked heavily. The arterial pressure had risen to over 200 mm within the past two years.

The patient was a well developed, highly nervous and irritable woman, appearing greatly depressed. The distribution of hair was normal. There was acne vulgaris over the skin of the face and chest. Examination of the fundi showed that the nerve heads were hyperemic but sharply outlined and without papilledema.

The arterioles were straightened and constricted (grade 2). An early stage of perivasculitis was present. The veins were dilated, and arteriovenous compression was observed. There was no hemorrhage or exudate. The thyroid gland was not enlarged. The heart was overactive and the rate 96. It was not enlarged. Roentgen measurements showed a total transverse diameter of 12.6 cm and an internal diameter of the chest of 23 cm. The first sound was snapping in character and was followed by a short systolic whiff. Both the aortic and the pulmonic second sound were markedly accentuated. The peripheral vessels were slightly thickened. Both the superficial and the deep reflexes were active but more so on the left than on the right. Roentgenograms of the skull disclosed that the vessels within the bone of the vault were markedly calcified. The sella turcica was normal. The pineal gland was calcified. There was no calcification of the peripheral vessels. The electrocardiograph record showed a positive T wave in leads I and II and a negative T wave in lead III, a PR interval of 0.16 second, preponderance of the left ventricle and a normal rhythm. After eight days of rest in bed the blood pressure varied from 240 to 170 mm systolic and from 138 to 112 mm diastolic, averaging 210 systolic and 130 diastolic. Intramuscular injections of colloidal sulfur and oral administration of sodium thiocyanate reduced the pressure slightly. The patient felt badly during most of her stay in the hospital, prostrating headaches alternating with severe mental depression. The level of the arterial pressure varied widely and showed little tendency to fall.

On Jan 7, 1935, the anterior nerve roots were severed from the eighth thoracic to the first lumbar segment, inclusive. The blood pressure fell to 90 systolic and 40 diastolic immediately after the operation and gradually rose to an average level of 148 systolic and 94 diastolic. Fecal and urinary incontinence developed but slowly disappeared. Bowel movements were obtained for a few weeks after the operation only by the use of enemas and injections of solution of posterior pituitary. It was found that the ethyl ester of betamethylcholine chloride often produced effective bowel movements.

The vital capacity before operation was 2,100 cc and after operation 1,500 cc. The waist measurement was 69.5 cm before operation and 75 cm after operation. Fluoroscopy of the diaphragm showed movement of 3 or 4 cm on both sides, which was unchanged after section of the roots. Tests showed that sweating was absent over an area of the skin of the abdomen extending from slightly below the costal margin to the pubis. Gastric analysis showed the presence of free hydrochloric acid and a total acidity of 105. After operation the total acidity was 108. Reexamination of the x-ray films showed that the right disk was still slightly hyperemic and the arterioles were no longer constricted. No arteriovenous compression was present. The size of the veins was normal, the change being marked in comparison with the preoperative status. The aortic and pulmonic second sounds were still accentuated. The mental depression continued for several months in spite of the fact that the blood pressure was not far above normal, but it was less marked. She still exhibited the attacks of blushing, lacrimation and palpitation, during which the arterial pressure rose to 180 systolic and 124 diastolic but they were not as intense as before the operation. She was uncooperative and continually had difficulty with other patients and nurses. Indeed, it was difficult to measure the blood pressure when she was not angry at something. It varied from 140 to 190 mm systolic and from 90 to 110 mm diastolic. The average pressure was 164 systolic and 110 diastolic nine months after operation but rose to 220 systolic and 122 diastolic, nine months later. After operation she had headaches rarely, and these were not severe. Nine months after operation her whole attitude seemed to change and she is now an agreeable person.

Comment—This was a case of severe hypertension in a girl with neurotic tendencies. Emotional instability and racing headaches were the outstanding symptoms. Six pairs of anterior nerve roots (eighth thoracic to first lumbar) were severed. The fall in blood pressure averaged 60 mm systolic and 25 mm diastolic. After nineteen months it slowly rose to a level a little below that observed before operation. The headaches largely disappeared, and she was able to resume her work as a nurse. The mental depression from which she suffered has almost disappeared, and on the whole she feels much improved.

CASE 9—A 26 year old housewife complained of blurring of the vision for one year. There was no vascular disease known in the family. She had had scarlet fever at the age of 14 years. Eight years before admission to the hospital she had consulted a physician because of burning and itching on urination, and sugar was found in the urine. It was possible to control the diabetes by means of diet. One year before admission to the hospital she missed a menstrual period. Two months later the arterial pressure was found to be 168 mm systolic. Protein was found in the urine. At that time she complained of dimness of vision, and a month later a hemorrhage was observed in the right fundus. A few weeks later another one occurred in the left fundus. Vision became steadily diminished until at the time of admission she was unable to distinguish objects held close to her eyes. At times swelling of the ankles occurred. Four months after she became pregnant an abortion was performed. Shortly before this an infection of the toe occurred, with cellulitis which spread up the leg, resulting in an abscess in the calf muscles. She noticed that after the abortion she became nervous, lacked ambition, tired easily and was unable to sleep normally. The menstrual periods became irregular, and she lacked libido. Nocturia also occurred. Eleven months after the onset of symptoms she entered the Presbyterian Hospital. Dr F D Mott and Dr Wilcox kindly furnished us with the following information. The blood pressure was 168 systolic and 90 diastolic. Partial detachment of the retina was observed, with marked exudation. Preretinal and vitreous hemorrhages also were noted. The blood sugar content was 170 mg per hundred cubic centimeters, and the creatinine content was 1.6 mg. The Wassermann reaction of the blood was negative. The basal metabolic rate was -6 per cent. During her stay of one month in the hospital the urea content rose from 55 to 84 mg per hundred cubic centimeters of blood. The patient's weight fell from 165 to 147 pounds (75 to 67 Kg).

Physical examination showed that the patient was short, overweight and almost blind. The distribution of hair was normal. The skin of the trunk was abnormally brown. The pupils reacted sluggishly to light. The patient could count fingers at 6 inches (15 cm). In the right eye was a large opacity in the vitreous and a deeper hemorrhage into the vitreous. There was extensive hemorrhage in the neuro-epithelial layers of the retina. Detachment of the retina had occurred in both fundi, and hemorrhages were present. The remnants of the vessels were tortuous and of uneven caliber. A purulent, necrotizing lesion of the gum margin was present, with erosion of the base of the teeth. The heart rate was 96. Measurements made on percussion showed it to be markedly enlarged to the left and to the right. The sounds were of good quality. The aortic and pulmonic second sounds were slightly accentuated. The arterial pressure was 198 systolic and 98 diastolic. The edge of the liver was palpated 2 cm below the costal margin.

The electrocardiogram showed a negative T wave in lead I and an upright T wave in leads II and III, notching of R₁ and preponderance of the left ventricle. The urea clearance on admission was 18 per cent of normal, but within fourteen days

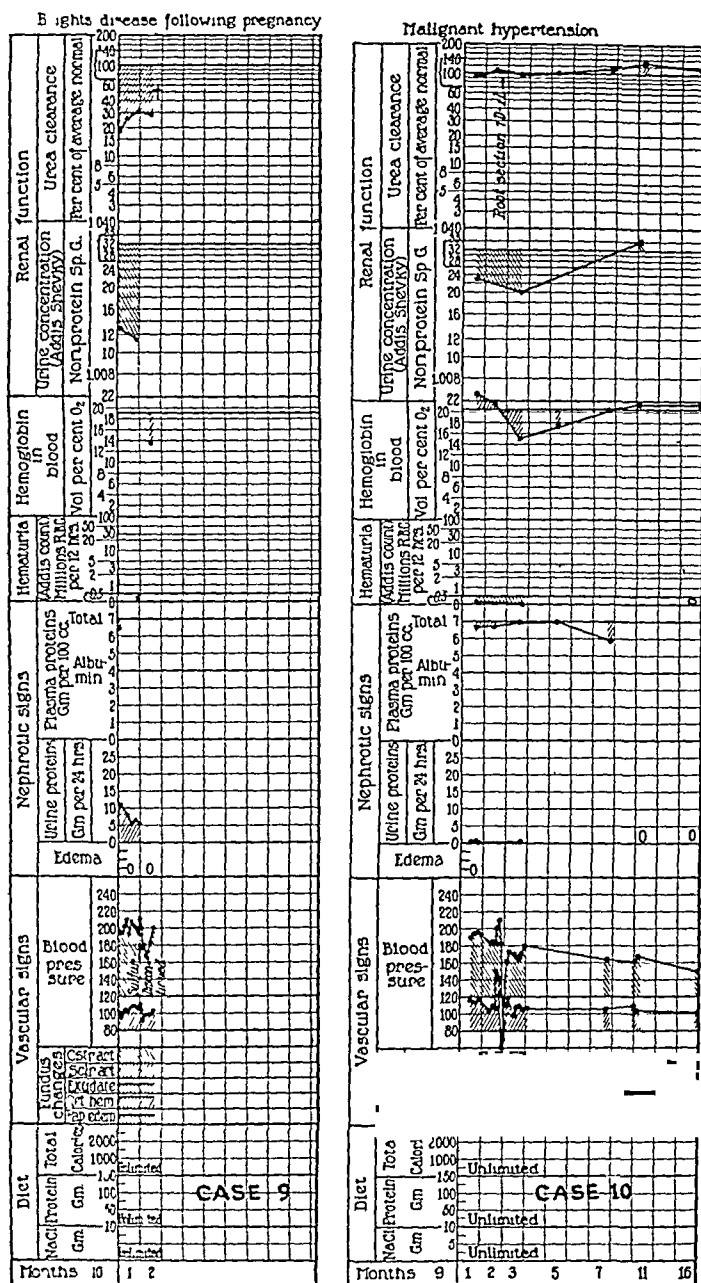


Fig 6—Case 9 was that of a woman aged 26 with Bright's disease and hypertension following pregnancy. She was 162 cm tall, and her ideal weight was 59.5 Kg. Case 10 was that of a man aged 24 with malignant hypertension. He was 176.5 cm tall and his ideal weight was 69 Kg.

it had risen to 26 per cent of normal. The blood pressure varied from 170 to 212 mm systolic and from 90 to 114 mm diastolic, averaging 200 systolic and 110 diastolic for a period of seven weeks in bed.

Comment—It was realized that this was a case of hopeless malignant arteriolar nephrosclerosis with neuroretinopathy, detachment of the retinas, cardiac hypertrophy and hypertension. It was not known whether reduction of the blood pressure would be of any value. As a last resort the patient was subjected to section of the anterior roots on June 20, 1934. During the latter part of the operation the blood pressure varied alarmingly. The roots from the sixth to the twelfth thoracic segment were severed. While the dura was being closed the patient stopped breathing. Dr. R. Parsons performed an autopsy. No hemorrhage was found in the cord. The primary diagnosis was generalized arteriolar sclerosis, arteriolar nephrosclerosis, arteriosclerosis with calcification of the aorta and its branches, detachment of the retinas with hemorrhage into them and partial atelectasis of the lungs. Accessory anatomic diagnoses were a persistent thymus gland, cholelithiasis and follicular cysts of the ovaries.

CASE 10—A 24 year old insurance clerk, referred to us by Dr. J. E. Hutchinson and Dr. T. H. Denne, of Hartford, Conn., complained of blurring of vision in both eyes and severe headaches for four and a half months before entry into the hospital. There was no familial history of hypertension. He was excitable and nervous. Eight months previously a stone had been removed from the pelvis of the right kidney. The blood pressure was normal at that time. Five weeks later he began to have dull headaches which appeared early in the morning and lasted until noon. These became progressively more severe. Three and one-half months later the vision in the right eye began to fail. Marked papilledema with hemorrhages and exudate was noted in the fundus of the right eye, and less marked changes were present in the left eye. Vision in the left eye was 20/20 and in the right eye 20/70. The basal metabolic rate was -4 per cent. The Wassermann reaction of the cerebrospinal fluid and blood was negative. The arterial blood pressure was 210 systolic and 140 diastolic. During the next four months the vision improved slightly, but the headaches continued. The patient had had no cardiac symptoms or signs.

Physical examination showed that the patient was a well developed man, who did not appear ill. There was bilateral papilledema (3 or 4 diopters). The disks were surrounded by large "cotton wool" exudates, and two hemorrhages were seen in the nasal portion of the left retina. The arterioles were irregular and constricted. The thyroid gland was not palpable. The heart was not enlarged. Measurements of the cardiac shadow on an x-ray plate showed a total transverse diameter of 13.1 cm. The internal diameter of the chest was 26 cm. The pulse rate was 86. The heart sounds were of good quality. The peripheral vessels were slightly thickened. The reflexes were hyperactive and equal on the two sides. An electrocardiogram showed a PR interval of 0.17 second, a positive T wave in leads I and II and a negative T wave in lead III and high voltage of the QRS complex in all leads. The sella turcica was normal in appearance on an x-ray plate. The blood sugar value was 86 mg. per hundred cubic centimeters. During twelve days of rest in bed the blood pressure varied from 182 to 232 mm. systolic and from 112 to 132 mm. diastolic, averaging 190 systolic and 120 diastolic.

On April 25, 1935, laminectomy was performed from the sixth dorsal to the first lumbar segment, and four days later the anterior nerve roots were severed.

from the ninth dorsal to the first lumbar segment, inclusive. The postoperative course was uneventful, and the patient was walking on the fourteenth day. All subjective complaints disappeared. The arterial blood pressure varied from 166 to 190 mm systolic and from 98 to 118 mm diastolic. The average pressure was 150 systolic and 100 diastolic fourteen months after the operation. The papilledema disappeared, the exudate in the retina was reabsorbed and the arterioles were not constricted. The basal metabolic rate was -3.5 per cent ten weeks after operation.

Comment—This was a case of malignant hypertension of short duration which advanced rapidly. The changes in the eyegrounds were marked and were the outstanding physical finding. The eyegrounds were normal nine months after operation. Five pairs of anterior nerve roots were severed. The patient recovered quickly from the operation, and all the subjective symptoms disappeared. A comparison of the level of the blood pressure when the patient was at rest in bed before the operation with that when he was up and about fourteen months after the operation showed that the pressure had fallen an average of 40 mm systolic and 20 mm diastolic. This man now lives an active outdoor life.

CASE 11—A 26 year old man, a clerk, who was referred to this hospital by Dr. Edward Saunders, complained of the sudden appearance of a blind spot in his right eye three weeks previously. There was no familial history of hypertension. The patient had always considered himself to be healthy. For the past two months he had noted that he became fatigued easily and that he had slight dyspnea on exertion. Nocturia also had occurred in the past month. No signs or symptoms other than these had been observed. Examination by Dr. Francis Glazebrook disclosed that the patient had proteinuria and hypertension.

The patient was well developed and appeared healthy. Examination of the fundi showed that papilledema (3 diopters) was present. The disks were surrounded by large areas of hard, white exudate which had coalesced, and throughout the retinas were small patches of exudate. The vessels which sprang from the disk were completely obliterated at many points. The arterioles showed all stages of constriction and degeneration, with perivascular reaction. The veins were dilated, tortuous and in many places markedly compressed by the arterioles. A well developed stellate figure was present in the macular region. The thyroid gland was normal. The heart was markedly enlarged both to the right and to the left. Measurements from an x-ray plate showed a total transverse diameter of 17.2 cm, with the internal diameter of the chest 27.4 cm. The aortic shadow appeared prominent and tortuous on the plate. The cardiac rate was increased (92 beats per minute) and there was a gallop rhythm. The aortic and pulmonic second sounds were both markedly accentuated, no murmurs were heard. Just inside the nipple line in the fifth interspace a friction rub was heard. The peripheral vessels were thickened (grade 2) and slightly tortuous. The electrocardiogram showed that the T wave was negative in leads I and II and upright in III. The conduction time was 0.2 second. There was marked preponderance of the left ventricle, and the rhythm was normal. An x-ray plate of the skull showed the sella turcica to be normal in appearance. The arterial blood pressure varied from a maximum of 210 to 166 mm systolic and from 152 to 110 mm diastolic during twenty-two days of rest in bed. The average pressure for this period was 190 systolic and 124

diastolic The Klein and Wassermann tests for syphilis were negative The blood sugar value was 102 mg per hundred cubic centimeters The basal metabolic rate was —8 per cent

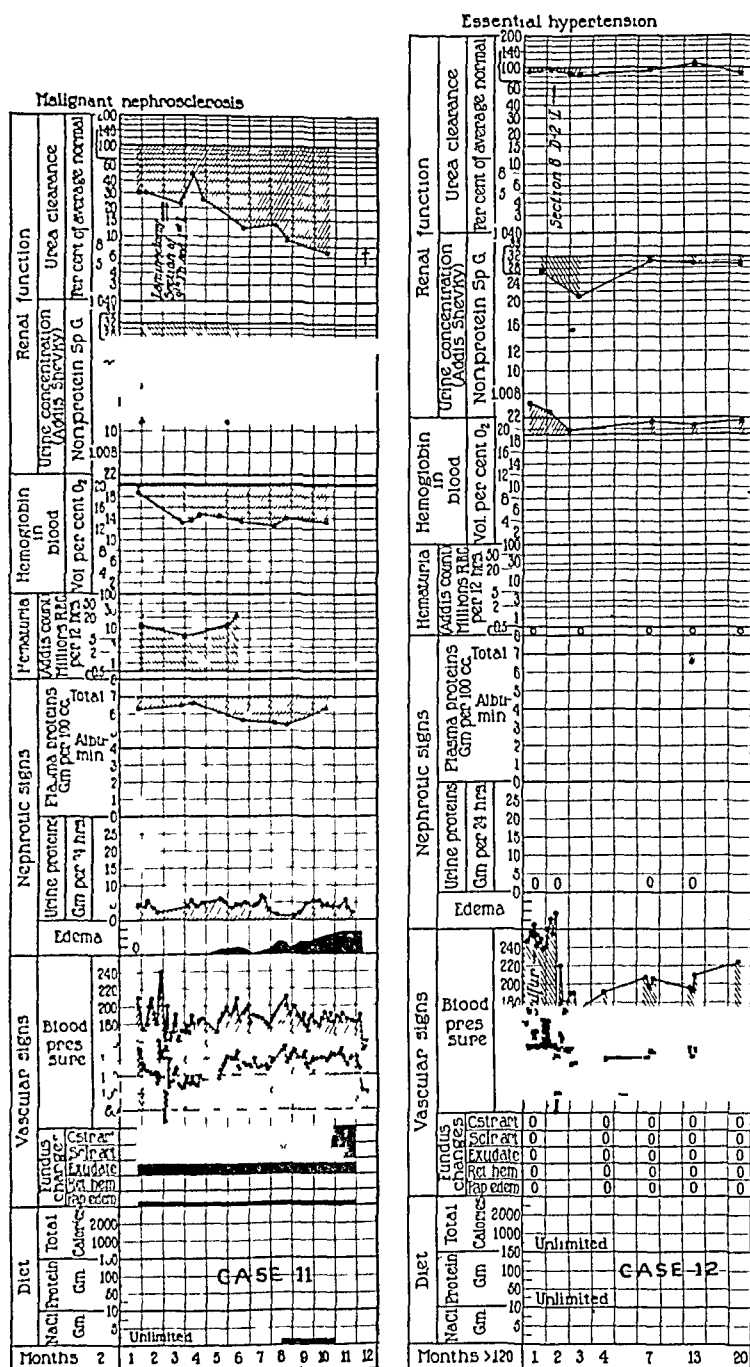


Fig 7—Case 11 was that of a man aged 26 with malignant nephrosclerosis. He was 182.5 cm tall, and his ideal weight was 73.5 Kg. Case 12 was that of a woman aged 33 with essential hypertension. She was 153.5 cm tall, and her ideal weight was 50.5 Kg.

On March 25, 1935, laminectomy from the sixth dorsal to the first lumbar vertebra was performed. Ten days later the anterior nerve roots were severed from the ninth dorsal to the first lumbar segment, inclusive. Recovery from the opera-

tion was uneventful. One month afterward measurements of the cardiac size from an x-ray plate showed a total transverse diameter of 16.5 cm, with the internal diameter of the chest 27.5 cm. The transverse diameter of the heart was 0.7 cm less than before operation. The T waves in leads I and II, which had been negative, became upright, and the atrioventricular conduction time was reduced from 0.2 to 0.16 second. Five months after the operation an electrocardiogram showed upright T waves in all three leads, a conduction time of 0.16 second, preponderance of the left ventricle and a normal rhythm. The basal metabolic rate was -4 per cent twenty-two days after the operation. Five weeks after the operation the fundi of the eyes appeared little changed from their condition before operation, but five weeks later the papilledema had disappeared. The arterial blood pressure varied from 160 to 210 mm systolic and from 98 to 142 mm diastolic. The average was 184 systolic and 122 diastolic. The patient was discharged but returned three weeks later, exhibiting signs of cardiac failure. This quickly disappeared with the aid of rest in bed and digitalis. The renal efficiency was somewhat more reduced, and the blood pressure had risen almost to its preoperative level and at times above it. The patient was readmitted six months after operation, again with cardiac failure. The renal efficiency fell progressively. Death occurred from both renal and cardiac failure ten months after the operation.

Autopsy (by Dr. C. P. Rhoads).—The heart was markedly hypertrophied (weight, 695 Gm.), especially the left ventricle. Coronary sclerosis (grade 3) was present. The renal arteries showed atheromatosis and moderate thickening. Marked atheromatosis (grade 3) was found also in the aorta, and atheromatous plaques studded the larger cerebral vessels. There was marked hyaline thickening of the vessels of the spleen, liver and pancreas.

The capsule of the kidneys was stripped with difficulty, leaving a pebbled surface. The cortex was atrophied. Microscopic examination showed advanced changes in the renal vessels, consisting of thickening with hyaline connective tissue and with hyaline replacement of the muscular tissue. Some of the glomeruli appeared normal, others showed deposits of fibrin in the capillary loops and still others were occluded by masses of hyaline tissue, proliferation of the capsule and adhesions between tuft and capsule.

The bone marrow showed slight interference with maturation of the cells. Many young forms were present, with few adult cells.

Careful examination of the spinal cord showed that no regeneration of the severed anterior nerve roots had occurred. Histologic examination was made by Dr. Lewis Stevenson, who made the following report:

"Sections stained with cresyl violet show a considerable loss of anterior and lateral horn cells, together with severe changes in the cells which remain. These changes are, for the most part, those seen in retrograde chromatolysis, with swelling of the cell, eccentricity or absence of the nucleus and fragmentation of the Nissl granules.

"The Loyez myelin sheath stain shows an absence or a severe degeneration in the fibers running from the anterior horns to form the anterior root. Many of the fibers in the anterior roots can be seen with this stain to be lacking in myelin sheaths. In addition to this there is an unexpected degeneration in the white matter of the cord in the spinocerebellar tracts, to some extent in the pyramidal tracts and here and there throughout the posterior columns. There is thickening of the wall of the anterior spinal artery, with a narrowing of its lumen. There is complete thrombosis of one of the other arteries in the posterolateral portion of one side of the spinal cord. There is a thickening of the wall of many of the smaller arteries in the meninges about the cord. Sections of the cord stained with



Fig 8 (case 11) —Section of the kidney showing marked vascular, tubular and interstitial changes Eosin and methylene blue stain, $\times 60$

hematoxylin and sudan III show some compound granular corpuscles in the spinocerebellar tracts on both sides, the anterior horns being singularly free from fat or fat-containing cells. Sections of the spinal cord stained for neuroglia show no increase in astrocytes or neuroglia fibers. The sections stained for microglia show no increase in this element.

"The posterior roots stained for myelin appear to be normal. The anterior roots, on the other hand, stained by the same method show marked degeneration of the myelin sheaths. Sections of the anterior root stained with the Cajal stain show few normal axis-cylinders and an increase in the nuclei of the neurilemma.

"Because of the absence of proliferation of the neuroglia in the degenerated portions of the spinal cord a Masson trichrome stain was used, and this shows a considerable deposit of green-staining collagen replacing the degenerated fibers in the white substance of the cord and also, to some extent, in the anterior horns of the cord."

Comment—This was a case of severe malignant hypertension, with a marked reduction in the renal efficiency. The exact time of onset cannot be stated, but the first symptom appeared only three weeks before the patient's admission to the hospital. Advanced morbid vascular changes had occurred and the heart and kidneys were seriously injured. The pathologic process in the kidneys was evidently active, because many red blood cells were being excreted as well as protein and large numbers of casts. We believed that the prognosis was hopeless and that death would not be long delayed. Only as a last resort was an operation performed. Five pairs of anterior nerve roots were severed in a two stage operation. For four months after the operation the patient continued to feel in excellent health. The average blood pressure fell 12 mm systolic and 9 mm diastolic, and the transverse diameter of the heart was reduced 0.7 cm. However, three months later there occurred cardiac decompensation, and there was evidence of further loss of renal efficiency. Both cardiac and renal failure progressed, terminating his life ten months after the operation. It was our opinion that the operation did not alter significantly the natural course of the disease. Autopsy confirmed the belief that morbid vascular change was widespread and severe. It proved also that after ten months no regeneration of the severed nerve roots had occurred. A corresponding loss of anterior and lateral horn cells was observed.

CASE 12—A housewife 33 years old, referred to us by Dr. J. V. Bohrer, complained of nervousness and easy fatigability. Up to the time of the present illness she was in good health but highly excitable. She had been pregnant three times but had had an abortion performed each time. Ten years before her admission to the hospital (1925) the arterial pressure was 240 systolic and 150 diastolic and varied from 184 systolic and 110 diastolic to 234 systolic and 134 diastolic during the next year. It was 190 systolic and 140 diastolic two years later (1928), 200 systolic and 145 diastolic in 1929, 238 systolic and 140 diastolic in 1933 and 240 systolic and 150 diastolic in 1934. A year and a half before her admission to the hospital, her brother died, and shortly thereafter she became excessively nervous.

She cried without reason and blushed abnormally often. Except for emotional instability and ready fatigability there were no symptoms.

The patient was a well developed, overweight Jewess, who appeared nervous. Throughout the examination she was never quiet. The eyegrounds were normal. The thyroid gland was slightly and diffusely enlarged (grade 1). Marked systolic thrusts were observed in the suprasternal notch. The heart was only slightly enlarged. Measurements from an x-ray plate showed a total transverse diameter of 13.7 cm and an internal diameter of the chest of 27 cm. The aorta was dilated (grade 2). There was a soft systolic murmur heard best to the left of the sternum in the fourth interspace and a second one heard over the base. The aortic second sound was slightly accentuated. The peripheral vessels were a little thickened. The deep reflexes were moderately hyperactive. Roentgen examination showed the sella turcica to be normal. An electrocardiogram exhibited a negative T wave in lead I, a diphasic T wave in lead II and an upright T wave in lead III, preponderance of the left ventricle and a normal rhythm. The renal efficiency was normal. The Kline test for syphilis was negative. The blood sugar value was 93 mg per hundred cubic centimeters. The arterial blood pressure varied from 246 to 272 mm systolic and from 132 to 150 mm diastolic, averaging 258 systolic and 140 diastolic. Daily intramuscular injections of 2 cc of colloidal sulfur produced no significant fall in the blood pressure. Even after the patient had spent five weeks in bed no reduction in pressure occurred, and the daily variations were surprisingly small.

On April 9, 1935, laminectomy was performed, and the anterior nerve roots were severed from the eighth thoracic to the first lumbar segment, inclusive. The postoperative course was uneventful.

Shortly after the operation the blood pressure varied widely but soon stabilized. During the next two months the systolic pressure varied from 170 to 200 mm and the diastolic pressure from 104 to 128 mm, averaging 182 systolic and 116 diastolic.

Comment—This is a rather unusual case of benign hypertension of at least ten years' duration in a young woman. Ten years before her admission to the hospital the arterial pressure was 240 systolic and 150 diastolic. In spite of continued high pressure, there was little evidence of cardiac, renal or vascular damage. The arterial pressure was fixed at a high level and was not influenced by rest, injections of sulfur or sedatives. Section of six pairs of anterior nerve roots was performed. The arterial pressure fluctuated widely for about fifteen days and then stabilized at an average level of 208 systolic and 126 diastolic for twelve months after the operation. The average pressure before the operation was 258 systolic and 140 diastolic.

CASE 13—A 46 year old man, a director of social work, referred by Dr. A. Tow and Dr. A. Fishberg, of New York, complained of easy fatigability for the past four years. Three of his sisters have moderate hypertension, and one brother had died of high blood pressure. This patient was ill with scarlet fever at the age of 3 years. He had always been overexcitable, highly emotional and impulsive. Sixteen years before his admission to the hospital his blood pressure was normal, but one year later it was 150 mm. Four years before his admission he noted that even moderate exertion caused extreme fatigue. Since then insomnia, irritability, loss of memory and a "sensation of pressure all over the body" had become increasingly

distressing. He had had a number of severe nosebleeds. Emotional instability was so marked that he was unable to adjust himself to his ordinary duties. One year before his admission to the hospital a hemorrhage was observed in the left fundus. Long periods of rest did not reduce the arterial pressure. He had complained of anginal pains in the past few months.

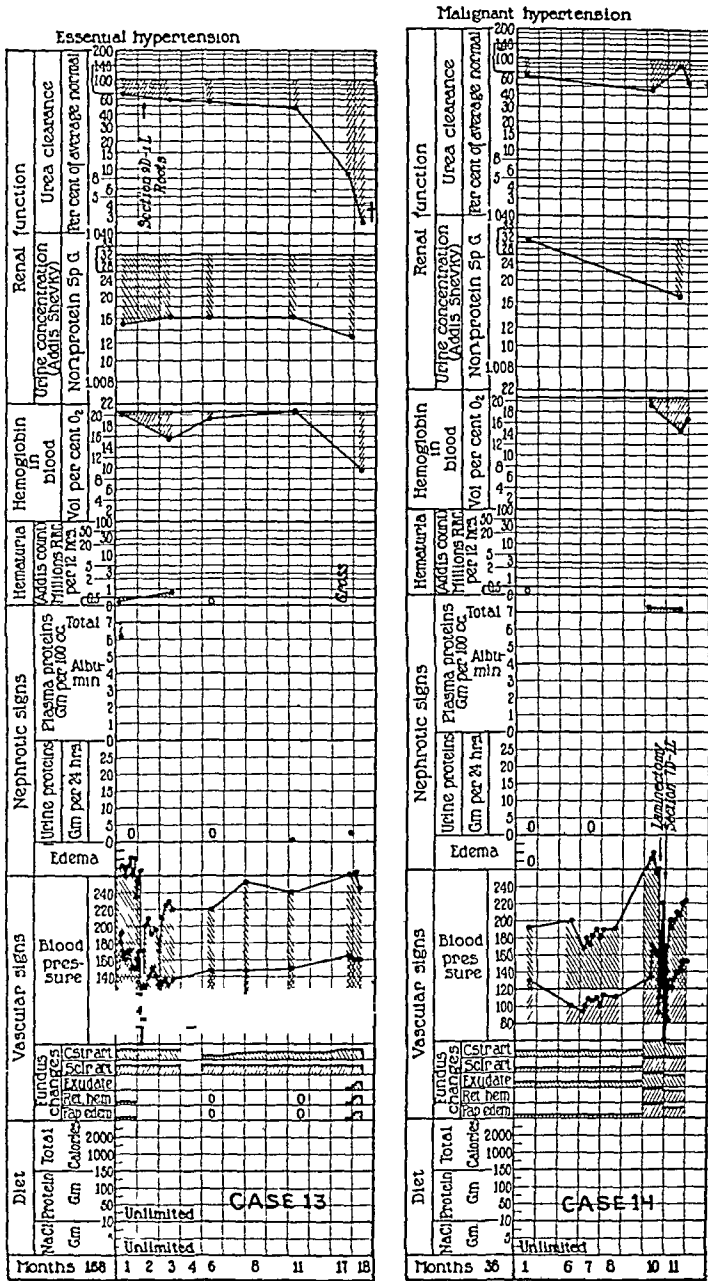


Fig 9—Case 13 was that of a man aged 46 with essential hypertension. He was 168 cm tall, and his ideal weight was 60.3 Kg. Case 14 was that of a man aged 37 with malignant hypertension. He was 169 cm tall, and his ideal weight was 64 Kg.

Physical examination showed a heavy-set middle-aged man, who did not appear ill but was restless and excited. The distribution of hair was normal. The disks

of the fundi were markedly hyperemic, and the edges were a little blurred. There was papilledema (grade 1). The arterioles were completely obliterated in many places, and some showed sausage-shaped constriction. They were tortuous (grade 3). The left inferior nasal artery was thrombosed. There was perivascularitis (grade 1) throughout the arteriolar tree and marked arteriovenous compression. The veins were moderately dilated and tortuous. In the left fundus there was a small flame-shaped hemorrhage, and throughout both fundi small areas of early exudate formation were seen. The heart was enlarged. Measurements from a roentgenogram showed a transverse diameter of 16.2 cm, with the internal diameter of the chest 27.5 cm. The aorta was tortuous and markedly dilated. The heart was boot shaped. The heart sounds were of good quality, and the aortic second sound was accentuated. The peripheral vessels were thickened (grade 2). All the reflexes were normal. The contour of the sella turcica was normal, the pineal gland was slightly calcified.

An electrocardiogram showed the T wave to be negative in lead I and positive in leads II and III. The auriculoventricular conduction time was 0.2 second, and preponderance of the left ventricle was present. Inhalation of a pearl of amyl nitrite reduced the arterial pressure from a control level of 250 systolic and 150 diastolic to a minimum of 204 systolic and 120 diastolic. Rest in bed with sedatives for thirty days did not reduce the arterial pressure significantly. During this period the pressure ranged from 232 to 280 mm systolic and from 140 to 192 mm diastolic, averaging 270 systolic and 160 diastolic.

On May 7, 1935, the anterior nerve roots were severed from the ninth thoracic to the first lumbar segment, inclusive. A moderate number of calcified plaques were found on the arachnoid membrane, and these made the operative procedure somewhat more difficult than usual. The blood pressure fell to 100 systolic and 70 diastolic, but the next day it rose to 170 systolic and 85 diastolic. Recovery from the operation was uneventful except for an episode suggestive of vascular collapse which occurred on the eighteenth postoperative day. Following a large defecation the patient felt weak and fainted. There were slight fever and leukocytosis, but no convincing evidence of coronary or pulmonary thrombosis was obtained. The arterial blood pressure fluctuated markedly for the first month after the operation but gradually stabilized at an average level of 240 systolic and 150 diastolic, with limits of from 220 to 260 mm systolic and from 110 to 160 mm diastolic. Slight regressive changes occurred in the eyegrounds, in that papilledema and the hemorrhage disappeared, otherwise they appeared to be unaltered. The size of the heart changed little. The vital capacity before operation was 3.4 liters, and seventeen days afterward it was 3.1 liters.

The patient lived an active and high strung life for the next sixteen months, when renal insufficiency rapidly appeared. He died seventeen months after operation. Autopsy showed that the vessels of most of the organs were markedly sclerosed. The kidneys in particular showed extensive vascular change.

Comment—This patient had suffered from hypertension for fifteen years. The blood pressure had become "fixed" at a high level (averaging 270 systolic and 160 diastolic), for it was not lowered by rest in bed or sedatives. Vascular damage had occurred in the cardiac, retinal, renal and peripheral blood vessels. In spite of its seeming fixity, the blood pressure fell to 100 systolic and 70 diastolic shortly after operation. Five pairs of anterior nerve roots (ninth thoracic to first lumbar) were

severed. Recovery from the operation was uneventful. After a period of marked fluctuation the arterial pressure became stabilized at an average level of 240 systolic and 150 diastolic. Practically all subjective symptoms disappeared, especially the headaches. The patient resumed his former work and felt that he had been markedly benefited, in spite of the fact that the reduction in the average arterial pressure was not great. Death occurred seventeen months after operation, with extreme renal insufficiency. While marked subjective improvement occurred, it is not known whether the length of life was prolonged, if so, certainly not greatly.

CASE 14—A 37 year old salesman, referred to us by Dr. C. Whiting, complained of severe headaches in the occipital region for the past two and one-half years. Five years before his admission to the hospital his blood pressure was normal. It was found to be 224 mm. fifteen months before admission. Three months later a hemorrhage occurred in the left fundus.

Physical examination showed extensive morbid changes in the eyegrounds. The heart was not overactive and was slightly if at all enlarged. On March 6, 1935, the total transverse diameter of the heart was 13.9 cm., and the internal diameter of the chest was 27 cm. The aorta was slightly dilated. An electrocardiogram showed only preponderance of the left ventricle at that time. The pineal gland was calcified, but the sella was normal. The blood pressure was 192 systolic and 130 diastolic. The patient was seen again nine months later, by this time the blood pressure had risen until it averaged 270 systolic and 170 diastolic with a maximum and a minimum systolic pressure of 280 and 262 mm. and a maximum and a minimum diastolic pressure of 186 and 160 mm., respectively. The papilledema was so intense that the nerve heads were literally mushroomed out into the posterior chamber. Hemorrhages and exudate were to be seen everywhere, except in the right eye, where the exudate was less extensive. The cardiac shadow was definitely enlarged, but much of the enlargement was due to widening and tortuosity of the aorta. Spinal puncture showed that the cerebrospinal fluid was under a pressure of 430 mm. of water. The cell count was not increased, but the protein content was definitely increased. In view of the remarkable rise in the arterial pressure and the advance in the morbid process in the eyegrounds, it was agreed that early fatal termination was probable. It was fully realized that operation was a last resort.

Laminectomy was performed on Dec. 23, 1935, from the fifth dorsal to the second lumbar vertebra, inclusive. On December 30 the nerve roots were sectioned from the seventh to the twelfth dorsal segment. The postoperative course was uneventful, and on the ninth day after the operation the patient was allowed up. Examination of the fundus one month later showed that the papilledema had markedly diminished. The other changes were so extensive that it was difficult to be certain whether there had been any change in them or not. Symptomatic relief was incomplete. The average arterial pressure was 210 systolic and 140 diastolic. Compound solution of iodine given in doses of 6 drops twice a day for fourteen days had slight, if any, effect on the rapid pulse rate. Two months after the operation the patient died with left hemiplegia.

Comment—This was a case of advanced malignant hypertension, and operation was undertaken only as a last resort. The arterial pres-

sion fell from an average preoperative level of 270 systolic and 170 diastolic to 210 systolic and 140 diastolic. Marked recession of the papilledema occurred. Symptomatic relief was incomplete. While the immediate effects of the operation were beneficial, the progress of the disease was not halted.

CASE 15—A 44 year old paper manufacturer, referred to us by Dr. T. Mackie, complained of headache and failing vision. There was a familial history of hypertension. The patient's health had always been excellent.

The patient had had repeated physical examinations, and until 1932 the blood pressure was normal. Shortly after that he began to have headaches, which had become more severe and frequent. The blood pressure was found to be slightly elevated, and after that it rose progressively. In January 1935 hemorrhages occurred in both eyes, with almost complete obliteration of the vision in the left eye. Headaches became more severe and at times were almost unbearable. Long periods of rest were not of any particular value either in relieving the headaches or in reducing the blood pressure.

Physical examination showed a well developed man, who did not appear ill. There was no evidence of the "diencephalic syndrome." Examination of the left fundus showed that the retina was almost completely obliterated with hemorrhage and exudate. Here and there a vein could be seen and an occasional arteriole, the latter being extremely contracted. The right eye also showed extensive retinal change. The arterioles were tortuous and frequently buried in the retinal bed. There was papilledema (grade 2). There were no fresh hemorrhages but considerable evidence of resorbing ones. The thyroid gland was not palpable. The heart was slightly enlarged on percussion. The heart rate was elevated, and the sounds were of good quality. An electrocardiogram showed evidence of myocardial damage. Measurements of the heart from a roentgenogram showed a total transverse diameter of 13.2 cm. The internal diameter of the chest was 28 cm., and the aorta showed a marked bulge. A roentgenogram of the skull showed that the sella turcica was large, and there appeared to be slight erosion of the posterior clinoid process. The pineal gland was calcified (grade 3). The cold-pressor test showed a markedly overactive response (a rise of 62 mm. systolic and 16 mm. diastolic). The arterial pressure over a period of nineteen days in bed varied from 168 to 222 mm. systolic and from 118 to 150 mm. diastolic. The average pressure was 200 systolic and 132 diastolic. In view of the extreme changes in the eyegrounds and the rapid progress of the disease, a diagnosis of malignant hypertension was made, and extensive laminectomy with section of the anterior nerve roots was advised as the only possible means of retarding the disease.

On Dec. 3, 1935, laminectomy was performed, and six days later the anterior nerve roots were severed on both sides from the eighth dorsal to the first lumbar segment, inclusive. The wound healed without difficulty, but the patient had a mental upset. For a time it appeared as though he had a true psychosis, but this gradually disappeared with the help of physical therapeutic methods and small amounts of sedatives. After three weeks he was himself again, and his progress was rapid. Two months after the operation there was definite improvement in the ocular fundi. Constriction of the arterioles had disappeared. There were no fresh hemorrhages or any new exudate. Slight papilledema was still present in

the right eye, and the old scar of the nerve head was visible in the left eye The cold-pressor test showed a response of 28 mm systolic and 26 mm diastolic There was no change in the renal efficiency There appeared to be marked subjective

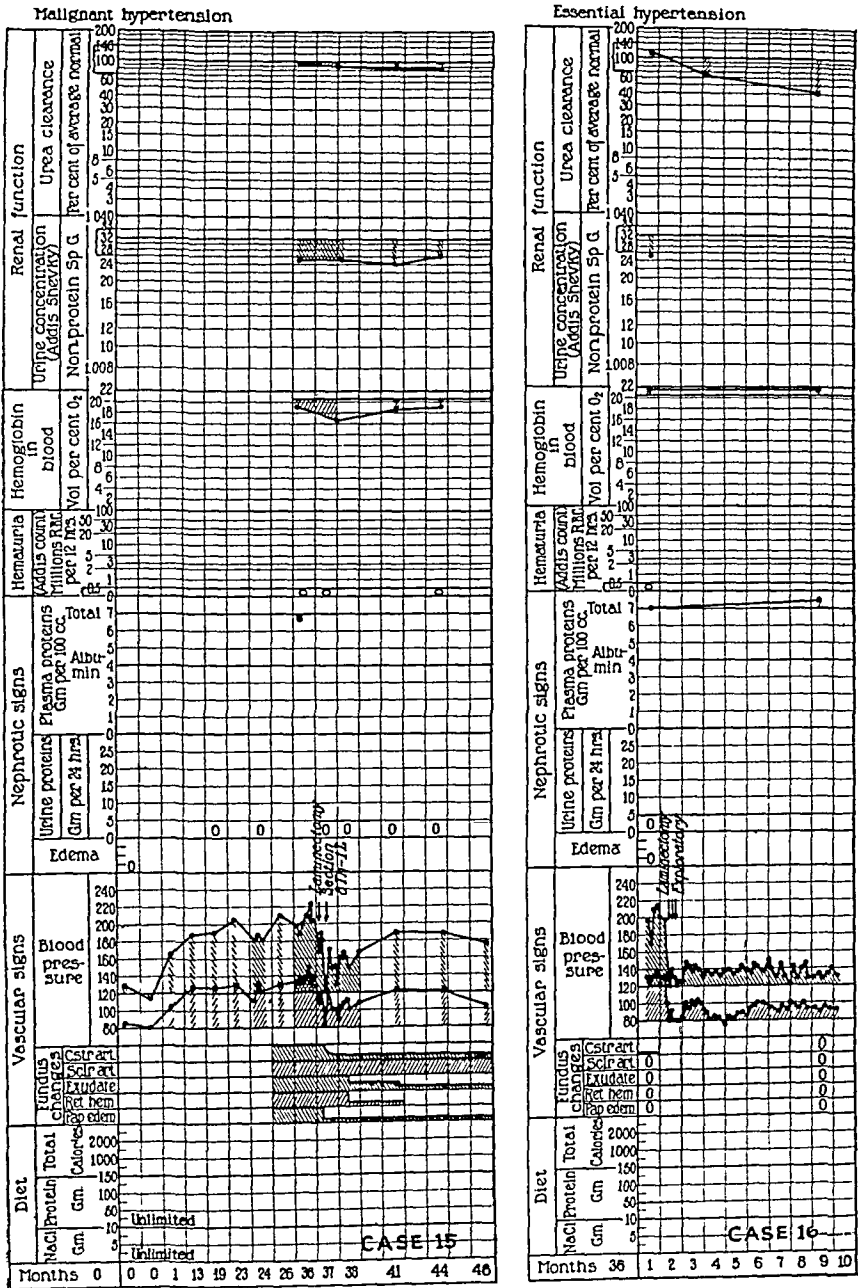


Fig 10—Case 15 was that of a man aged 44 with malignant hypertension He was 175 cm tall, and his ideal weight was 67.8 Kg Case 16 was that of a man aged 21 with essential hypertension He was 172 cm tall, and his ideal weight was 66 Kg

improvement The arterial pressure varied from 130 to 194 mm systolic and from 90 to 120 mm diastolic. The average pressure was 186 systolic and 120 diastolic seven months after the operation

Comment—This was a case of severe malignant hypertension. Operation resulted in symptomatic relief. The arterial pressure fell from an average preoperative level of 208 systolic and 136 diastolic to 186 systolic and 120 diastolic. Marked regression in the morbid changes in the eyegrounds occurred. Thirteen months after operation the systolic blood pressure had risen to a level only slightly below the preoperative level, but the diastolic pressure was 30 mm or more lower. It is our opinion that the rapid progress of the disease was markedly retarded but that the ultimate prognosis may be poor.

CASE 16—A 21 year old man, referred to us by Dr. F. M. Hanes and Dr. E. L. Persons, of Durham, N. C., had no complaints. There was no familial history of hypertension.

This patient was impulsive and overexcitable, but from all outward appearances he seemed to be a perfectly normal college student. By chance during the course of a routine physical examination when he was 18 hypertension was discovered. The blood pressure two years later was found to be 200 systolic and 133 diastolic. The heart and eyegrounds were normal. The patient was admitted to a hospital, and the blood pressure was found to be 220 systolic and 152 diastolic. Other examinations, including the Wassermann and Kahn tests, revealed no abnormality. During the course of the year the heart was found to have enlarged. The basal metabolic rate was $+7$. An electrocardiogram was suggestive of myocardial damage, because the T waves in leads I and II were inverted, and the T wave in lead IV was diphasic along with a levogram. Fresh hemorrhages were found in the retina. Since there was no significant fall in the blood pressure and the pressure remained at a dangerously high level, he was referred to this hospital for examination.

Physical examination showed an unusually well built, well developed man who did not appear ill. The arterioles of the fundi showed sausage-shaped constrictions, but the retinas were otherwise normal. The heart appeared slightly if at all enlarged. The aorta was dilated (grade 2). The peripheral vessels were thickened (grade 1). A roentgenogram of the skull showed that the contour and density of the sella were normal. The response to the cold-pressor test was marked, the systolic pressure rising to 50 mm and the diastolic to 48 mm. The arterial pressure varied from 170 to 210 mm systolic and from 122 to 140 mm diastolic, with an average of 200 systolic and 132 diastolic over a period of three weeks.

On Jan. 6, 1936, laminectomy was performed from the sixth dorsal to the second vertebra, inclusive. The following day the patient was paralyzed in both legs. The wound was opened, and a blood clot was removed, which may have been compressing the cord. Since an immediate return of function did not occur, the wound was reopened and the dura and cord were carefully inspected, but no abnormality was noted. After two months, slight sensation returned, and in four months there appeared to be slight voluntary movement. It is too early to predict how much function will return. The blood pressure has been markedly reduced, the average being 140 systolic and 100 diastolic.

Comment—This was a case of relatively early essential hypertension in which the arterial pressure was rapidly rising and in which cardiac changes were already present. The fact that hemorrhages were observed

in the eyegrounds at one time suggests that the disease might be malignant. After operation transverse myelitis developed, possibly as a result of pressure from a blood clot. After two months slight sensation in the legs returned and after four months slight motor power. It is too early to be certain of the outcome of this serious accident. The arterial blood pressure has been sharply reduced.

CASE 17—A 37 year old broker complained of severe headaches for the past eight years. In January 1928, during a casual examination, his blood pressure was found to be 145 systolic and 100 diastolic. Shortly following this, as a result of the stock-market crash, the patient went through a long period of intense overwork and worry. He became nervous and was unable to sleep. It was found that his blood pressure was slowly rising. In December 1931 Dr. George Crile performed bilateral adrenal denervation. The operation had no effect either on the symptoms or the level of the blood pressure. The patient gave up work entirely because of headaches and nervousness. He had some signs and symptoms of the "diencephalic syndrome."

Physical examination showed that the vessels of the eyegrounds were slightly constricted (grade 1) and a little tortuous in some places, but usually the course was normal. The heart was boot shaped and enlarged (grade 2). The peripheral vessels were thickened (grade 1). A roentgenogram of the heart showed that the total transverse diameter was 14.5 cm. and that the internal diameter of the chest was 26 cm. Of especial interest is the fact that the aorta was markedly and diffusely dilated. A roentgenogram showed that the sella turcica was normal. The blood pressure throughout the patient's stay of twenty-five days in bed averaged 230 systolic and 140 diastolic, the maximum and the minimum systolic pressure being 278 and 210 mm. and the maximum and the minimum diastolic pressure 150 and 120 mm., respectively. The cold-pressor test showed a response of 56 mm. systolic and 28 mm. diastolic pressure. The patient cooperated well in trying the "progressive relaxation" treatment. He learned a great deal from it, and we believe that the maximum fall in blood pressure that could be expected was obtained.

On Feb. 3, 1936, laminectomy from the sixth dorsal to the second lumbar vertebrae was performed. The postoperative course was uneventful, except that the patient refused to have the second stage of the operation performed, that is, have the dura opened and the nerve roots severed. Every effort was made to induce him to have the operation completed. He was up in a chair fourteen days after the operation. The arterial blood pressure soon rose to the preoperative level. Some symptomatic relief occurred, but it lasted only a few months.

Comment—This was a case of essential hypertension with moderately disabling symptoms. Adrenal denervation performed elsewhere did not reduce the arterial pressure or relieve the symptoms. "Progressive relaxation" was tried with what appeared to be only moderate success. Laminectomy was performed, and for reasons of his own the patient refused to allow the second stage of the operation to be performed, i. e., exposure of the cord and section of the roots. He therefore voluntarily acted as a control for our series of cases. The arterial pressure soon rose to the preoperative level. Four months

after the operation it was above the preoperative level, and fresh hemorhages, exudate and papilledema had appeared in the eyegrounds. When last heard from (seven months after the operation) the patient was obviously in the terminal phase of the disease.

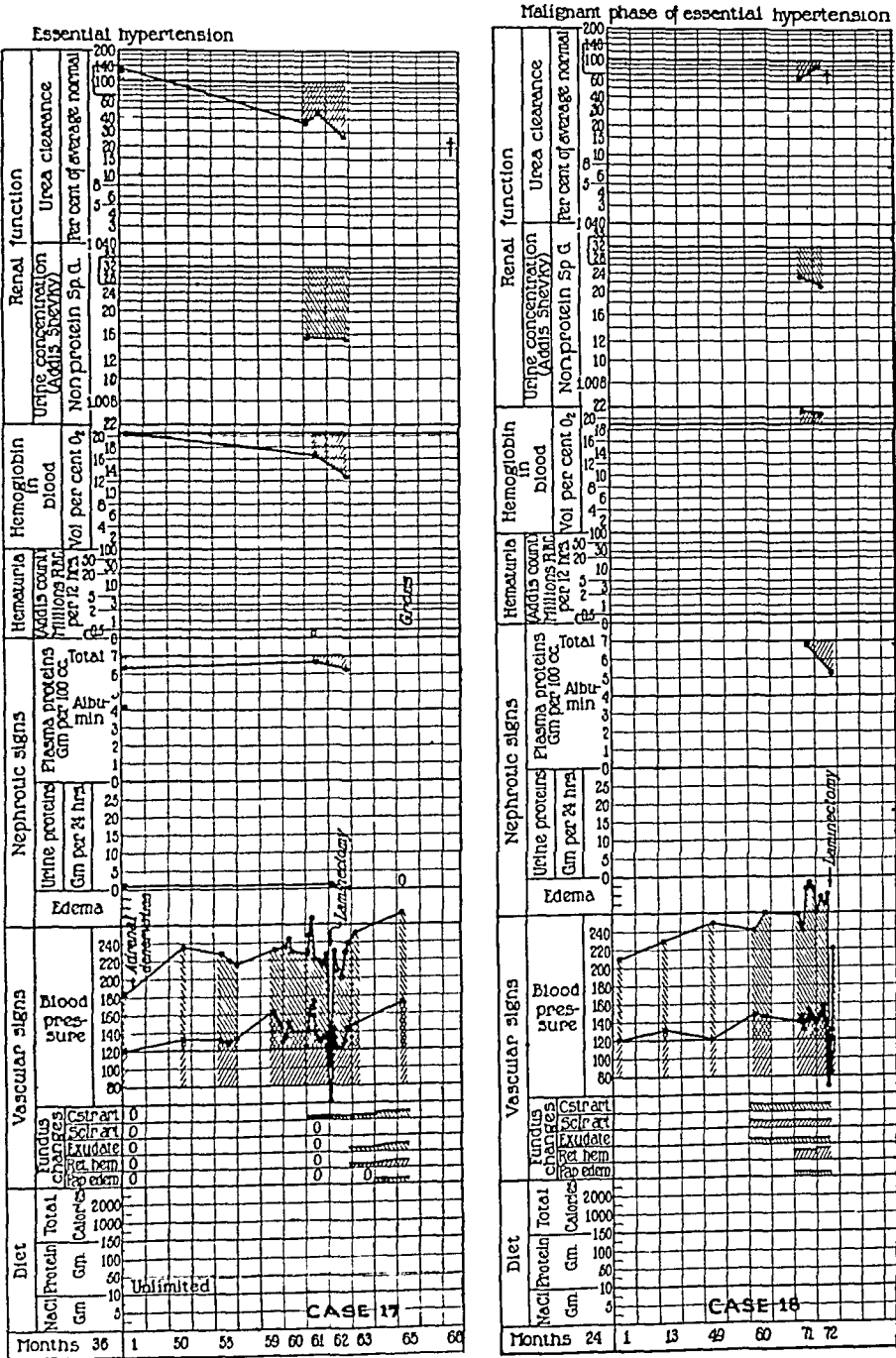


Fig 11—Case 17 was that of a man aged 37 with essential hypertension. He was 171.5 cm tall, and his ideal weight was 70 Kg. Case 18 was that of a woman aged 39 with essential hypertension in the malignant phase. She was 148 cm tall, and her ideal weight was 52.5 Kg.

CASE 18—The complete history of this 39 year old woman will not be presented. She died as a result of septicemia due to the hemolytic streptococcus three days after laminectomy was performed. Hypertension had been discovered six months before she was admitted to the hospital. Fresh hemorrhages and exudates were observed in the ocular fundi, with papilledema. Moderate cardiac hypertrophy and dilatation of the aorta were noted. The renal function was slightly reduced (the urea clearance was 81 per cent of normal, and the maximum concentrating ability was 1 023). The average arterial pressure was 270 systolic and 148 diastolic over a period of five weeks while the patient was in bed.

Laminectomy was performed, but the dura was not opened. The following day it was observed that the patient's neck was stiff and that she was confused mentally. Almost complete anuria followed (the urea clearance was 42 per cent of normal). The extremities were pale and bloodless. Culture of the blood and spinal fluid showed the presence of hemolytic streptococci of group A (Lancefield)²⁸. Transfusions of blood and the intravenous injection of solutions of sodium lactate, sodium chloride and dextrose were associated with reestablishment of the urinary flow. The urea nitrogen content rose to a maximum of 83 mg per hundred cubic centimeters of blood, and there was 15.24 millimols of carbon dioxide per liter of blood. The latter value rose to normal, and the urea nitrogen value fell. In spite of the reestablishment of more normal urinary function the patient passed into a coma and died three days after the operation.

Autopsy limited to the incision made at operation showed streptococcic meningitis. The adrenal glands appeared normal except for a small adenoma. The kidneys were swollen, pale and soft, and the line of division between the cortex and the medulla was indistinct. Culture of material from the cord showed group A hemolytic streptococci.

CASE 19—This patient, a 22 year old housewife, had no complaints. In July 1929 her blood pressure was found to be normal. She was examined every six months thereafter until 1933, and the pressure was never found elevated. At that time she became pregnant, and during the course of pregnancy she was told that hypertension and proteinuria had developed. The pregnancy ended in a miscarriage. In October 1934 she was again pregnant. The blood pressure was found to be 280 mm. Severe headaches appeared.

Physical examination showed a well developed, slightly obese woman, who did not appear ill. Examination of the fundus revealed grade 3 constriction of the arterioles, many of them showing well defined sausage-shaped constriction. These vessels were slightly more tortuous than normal. The veins were dilated (grade 2). The physiologic cupping was unusually deep, and the nerve head was a little wider and more pale than normal. The heart did not appear to be laboring excessively. The sounds were of good quality. There was grade 1 to 2 enlargement. The aorta was markedly elongated and tortuous but not dilated. A roentgenogram of the skull showed that the sella was normal and that the pineal gland was not calcified. The cold-pressor test showed a maximum rise in systolic pressure of 20 mm and in diastolic pressure of 10 mm. The renal efficiency was markedly reduced. The maximum and the minimum systolic blood pressure were 290 and 230 mm (average, 260 mm), and the maximum and the minimum diastolic pressure were 180 and 122 mm (average, 160 mm), respectively. During her stay in the hospital severe secondary glaucoma developed. It did not respond to treatment with hot compresses and physostigmine.

28 The streptococci were typed by Mrs. R. Lancefield.

Section of the anterior root was performed on April 25, 1936 The patient bore the operation exceptionally easily and on the ninth day was up and about Shortly after the operation it was found that the intra-ocular tension in both eyes was normal Examination of the fundi showed that the secondary glaucoma had entirely disappeared and that there was slight secondary atrophy of the nerve head in the left eye The arterioles showed grade 2 constriction and in many places

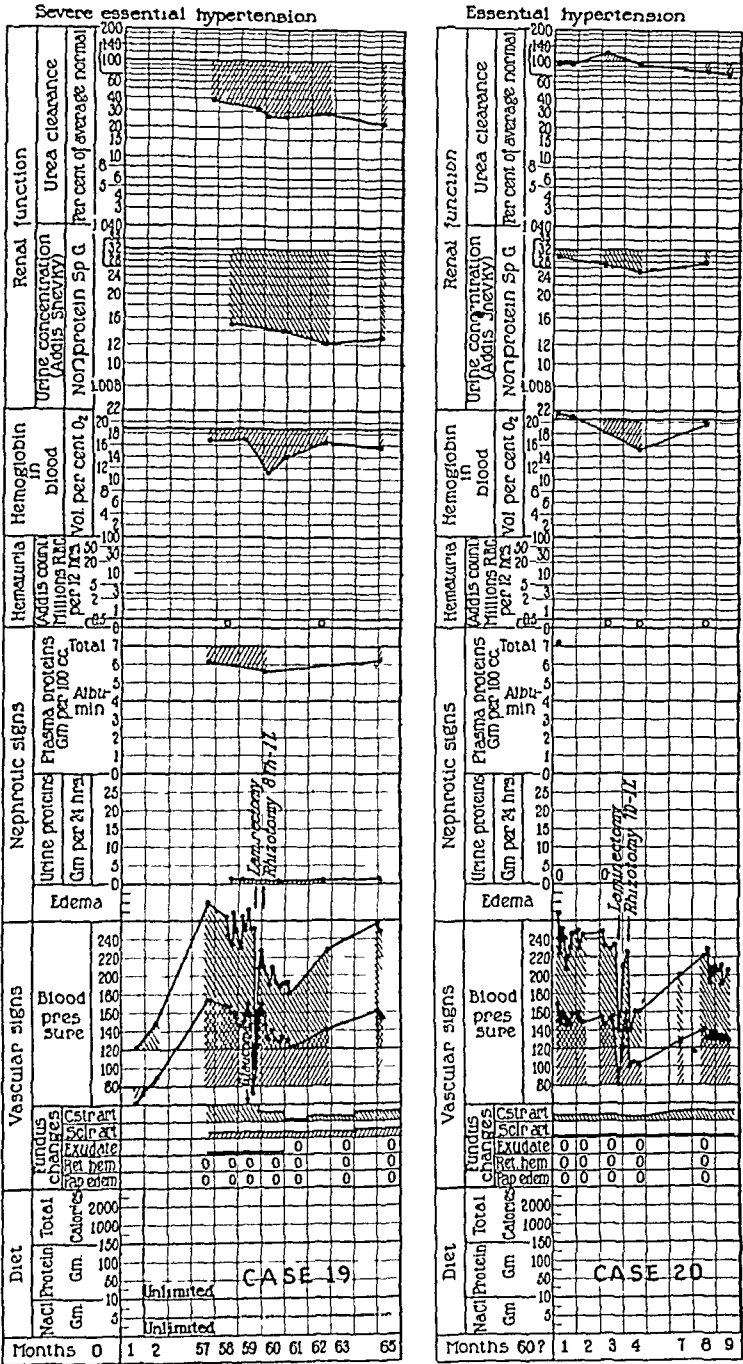


Fig 12—Case 19 was that of a woman aged 22 with severe essential hypertension She was 167 cm tall, and her ideal weight was 63 Kg Case 20 was that of a man aged 40 with essential hypertension He was 169 cm tall, and his ideal weight was 64 Kg

were tortuous. There were no hemorrhages, but there were points suggestive of an early hard, white exudate formation. The blood pressure fell to an average level of 192 systolic and 130 diastolic for a period of two and one-half months, but during the ensuing four months it rose to 256 systolic and 156 diastolic. The glaucoma has not reappeared, and the headaches occur only occasionally. It is apparent, however, that the beneficial effects of the operation as regards the blood pressure may be temporary.

Comment—This was a case of severe essential hypertension beginning during pregnancy. The arterial pressure was persistently high (260 systolic and 160 diastolic) in spite of rest in bed and sedatives. Secondary glaucoma developed while the patient was receiving treatment in the hospital. Convalescence from the operation was exceptionally easy. The glaucoma and headaches disappeared immediately after the operation. The arterial pressure was reduced to an average of 192 systolic and 130 diastolic for two and one-half months, but nine months after the operation it had returned to an average level of 230 systolic and 142 diastolic. The beneficial effects of the operation may be only temporary.

CASE 20—A 40 year old man had complained for at least a year of fatigue, dizziness and attacks during which unconsciousness occurred. Recently headaches had occurred sometimes lasting for three or four days. There have been no signs or symptoms of the "hypertensive diencephalic syndrome." Often he had pains just below the heart that caused him great alarm. One year before his admission to the hospital the blood pressure was found to range from 220 systolic and 150 diastolic to 158 systolic and 124 diastolic. Three months before his admission to the hospital he noticed for the first time transient paralysis of the left arm associated with unconsciousness which lasted for a few hours.

Physical examination showed a middle-aged man who did not appear ill. Examination of the fundus revealed that the nerve heads were hyperemic (grade 1). The arterioles were constricted (grade 2 to 3), with slight tortuosity and little perivascular reaction. There was slight arteriovenous constriction (grade 1), but no exudate or hemorrhage was present. There was a marked thrust in the jugular notch. Percussion showed the heart to be somewhat boot shaped. The heart sounds were of good quality. The aortic second sound was markedly accentuated. The peripheral vessels were thickened (grade 1). A roentgenogram of the skull showed a normal sella. The pineal gland was calcified (grade 1). The cold-pressor test showed a rise of 20 systolic and 26 diastolic. The maximum systolic pressure was 280 mm and the minimum 156 mm. The maximum diastolic pressure was 164 mm and the minimum 116 mm, with an average of 240 systolic and 150 diastolic. The fluctuations in blood pressure were wide.

Section of the anterior roots from the seventh thoracic to the first lumbar segment was performed on May 3, 1936. Nine days postoperatively the patient was up and feeling well. Examination of the fundi two weeks after the operation showed in some places grade 2 and 3 constriction, but the sausage-shaped constriction which was present before operation had disappeared. The patient had had no headaches. The cold-pressor test showed a systolic rise of 4 mm, and no diastolic rise. The average blood pressure was 210 systolic and 132 diastolic. At the time of his discharge the patient was considered to be improved.

Comment—This was a case of severe essential hypertension in a middle-aged man. Attacks of unconsciousness with transient paralysis caused him great distress. Section of the nerve roots was well borne and was associated with a fall in the average arterial pressure from 240 systolic and 150 diastolic to 210 systolic and 132 diastolic. No attacks have occurred during the six months since operation.

BIOPSY OF MUSCLE REMOVED AT OPERATION

Dr. C. P. Rhoads examined the specimens removed from the lumbar muscles at operation and stated that, except in cases 2, 5 and 12, morbid changes in the arterioles were not seen. It is of interest to note that two patients with malignant hypertension and two with so-called "fixed" hypertension exhibited no significant morphologic changes.

COMPLICATIONS ASSOCIATED WITH THE OPERATION

While in most cases recovery from operation was uneventful, in a few serious difficulties occurred. One patient (case 9) died just after closure of the dura. She might have survived the two stage operation as it is now our custom to perform it. A second patient (case 18) died as the result of septicemia due to a hemolytic streptococcus three days after laminectomy was performed. The dura had not been opened. The streptococcus proved to belong to the Lancefield group A. We have been unable to ascertain the source of the infection. Since the operation was performed in February, at the height of the season for infections of the upper respiratory tract, it suggests that, if elective, operation should be postponed until infections are not prevalent.

Transverse myelitis with paralysis of both legs occurred in one patient (case 16) eighteen hours after the laminectomy. The dura was not opened. At a second operation a moderate amount of blood clot was removed which may have pressed on the cord. As recovery was not immediate, the dura was opened at a third operation, and the cord was carefully inspected. None of us could see any change in its appearance which was considered abnormal. Slight sensation in the legs has slowly returned, together with slight motor function. It is our belief at present that recovery will be only partial.

One patient (case 15) was irrational during part of each night for two weeks after the operation and then recovered fully. The operation appeared to be associated with the release of a flood of deeply suppressed thoughts. Physical therapeutic measures, such as warm baths, thermal light treatment and massage, were of value in quieting him.

COMMENT

Seventeen patients have been subjected to section of the anterior nerve roots. The character of the disease has varied greatly (table 1).

TABLE 1—Summary of the Clinical Data for Patients in Whom Section of the Anterior Roots Was Performed

Case	Sex	Age	Duration of Hypertension	Retinal Changes	Cardiac Changes	Urea Clearance, % of Normal	Blood Pressure Before Operation, Mm of Mercury			Number of Pairs of Anterior Nerve Roots Sectioned	Level of Roots Sectioned	Date of Operation	Blood Pressure After Operation, Mm of Mercury			Period of Observation After Operation, Months	Subjective Improvement
							Average	Maximum	Minimum				Average	Maximum	Minimum		
Group 1 Severe Benign Hypertension with Moderate Vascular Changes																	
12	F	33	>10 yr	0	++	90	253/140	272/150	246/132	6	8Th 1L	4/ 9/35	182/116	200/128	170/104	5	Moderate
19	F	22	2 yr	++	+	31	260/160	290/180	230/122	6	8Th 1L	5/ 1/36	210/138	200/120	160/98	4	Marked
20	M	40	3 yr	0	+	92	240/150	280/164	156/116	7	7Th 1L	5/ 4/36	160/116	180/134	154/110	2	Marked
Group 2 Severe Benign Hypertension with Marked Vascular Changes																	
6	F	40	>2 yr	++	++	72	230/142	260/160	208/132	4	9Th 12Th	3/ 7/35	210/122	260/146	180/110	10	Marked
7	F	35	>3 yr	++	++	88	190/122	212/132	182/108	6	7Th 12Th	1/25/35	176/114	200/120	160/98	4	Marked
13	M	46	15 yr	++	++	68	270/160	280/192	232/160	5	9Th 1L	5/ 7/35	230/142	250/150	220/110	10	Marked
Group 3 Hypertension in Young Women Exhibiting the "Hypertensive Diencephalic Syndrome"																	
1	F	23	>18 mo	0	0	104	190/122	200/140	162/108	9	6Th 2L	5/11/34	150/96	170/104	110/70	29	Very marked
2	F	24	+2 yr	+	0	80	106/149	220/160	180/130	5	9Th 1L	11/ 2/34	162/98	180/112	120/80	16	Very marked
3	F	17	18 mo	++	0	106	180/122	210/144	136/94	5	9Th 1L	12/18/34	140/90	152/100	122/70	19	Very marked
4	F	32	8 yr	0	0	101	210/130	230/145	176/126	5	9Th 1L	11/30/34	154/104	186/120	140/92	15	Marked
5	F	25	3 yr	+	0	91	184/116	264/148	148/90	9	6Th 2L	10/29/34	156/106	170/120	140/90	12	Marked
8	F	25	2 yr	++	+	74	210/130	240/138	170/112	6	8Th 1L	1/ 7/35	182/118	220/128	120/90	13	Marked
Group 4 Malignant Hypertension																	
9	F	26	>1 yr	+++	+++	18	200/110	212/114	170/90	7	6Th 12Th	6/20/34	Patient died shortly after the dura was closed			14	Marked
10	M	24	7 mo	+++	+	92	190/120	232/132	182/112	5	9Th 1L	4/25/35	150/100	190/118	146/98	10	No symptoms present before operation
11	M	26	+3 mo	+++	+++	30	190/124	210/152	166/110	5	9Th 1L	3/25/35	160/138	210/154	160/98	10	Moderate
14	M	37	>2 yr	+++	++	55	270/170	280/186	262/160	6	7Th 12Th	12/30/35	210/140	222/156	190/120	1	Marked
15	M	41	3 yr	+++	++	88	208/136	222/150	168/118	6	8Th 1L	12/ 3/35	186/120	190/122	140/90	7	Marked
Group 5 Patients in Whom Laminectomy but Not Root Section Was Performed																	
16	M	21	2 yr	0	+	119	200/132	210/140	170/122	0		1/ 6/36	140/100	150/114	110/70	8	No symptoms before operation
17	M	37	7 yr	+	+	42	230/140	278/150	210/120	0		2/ 3/36	240/146	260/154	220/130	4	Questionable
18	F	39	6 yr	+++	+++	86	270/148	290/160	230/132	0		2/19/36				Died of streptococcal meningitis	

* The cases are grouped according to the character of the disease

In one the disease was moderately benign but of long standing, in some it was of short duration and highly malignant, while in others, besides hypertension, a reduction in the renal efficiency was marked ("nephrosclerosis") The results of operation are correspondingly not comparable within the entire group

Three patients (cases 12, 19 and 20) showed severe but benign involvement, with moderate vascular change There was variation as to the rate at which the morbid process was advancing The arterial pressure was uniformly unusually high, yet symptoms were not especially marked In one patient (case 19) severe secondary glaucoma developed, and one (case 20) had a series of attacks resembling transient apoplexy Section of the roots in these cases has produced benefit, although it appears to be temporary

Six patients (cases 1 to 5 and 8) exemplify a type of hypertension commonly found in young women All were less than 32 years of age Renal and cardiac changes were minimal, but constriction of the retinal arterioles was easily observed Symptoms such as headache and shortness of breath were present and usually severe Especially marked were symptoms which have been grouped under the term hypertensive diencephalic syndrome²⁹ Section of from five to nine pairs of nerve roots resulted in a pronounced fall in the arterial pressure Many of the subjective symptoms disappeared, especially headache and palpitation The "diencephalic symptoms" were less obviously influenced This group of patients appeared markedly benefited

Three patients (cases 6, 7 and 13) suffered from benign essential hypertension of long duration Evidence of marked vascular change was found on examination of the eyegrounds and the peripheral vessels and in the sections of muscle removed at operation Cardiac changes were present, as shown by the electrocardiograms, the roentgenograms and the symptoms and signs which developed when the heart was under slight strain The renal efficiency, as estimated by the ability to concentrate urine and the urea clearance test, was moderately reduced The arterial pressure, especially the diastolic, was regularly high The diastolic pressure was as high as 192 mm in one patient (case 13) Four pairs of nerve roots were severed in one patient (case 6), five pairs in another (case 13) and six pairs in the last (case 7) The arterial pressure fell definitely but by no means to normal Subjective improvement was marked The patient (case 6) in whom only four pairs of roots were cut died of apoplexy nine months after the operation The other (case 13) actively engaged in his business for a year but died with renal insufficiency seventeen months after operation The

29 Page, I H A Syndrome Simulating Diencephalic Stimulation Occurring in Patients with Essential Hypertension, *Am J M Sc* **190** 9, 1935

last patient is doing well two years after operation. It is our opinion that the reduction of pressure from such excessively high levels may reduce the strain on the heart and blood vessels sufficiently to prolong life somewhat but that only in exceptional cases are the risks of operation justified.

The last group, consisting of three young and two middle-aged patients (cases 9, 10, 11, 14 and 15), had highly malignant types of hypertension. The disease was of short duration, but within this period the vascular damage was extreme. Marked neuroretinopathy was present in all these patients. In two the cardiac and renal changes were advanced, in two they were moderate, and in one they had just appeared. Five pairs of anterior nerve roots were severed in each of two patients (cases 10 and 11), six pairs in two (cases 14 and 15) and seven pairs in the other (case 9). One patient (case 9) died shortly after closure of the dura. Autopsy showed no hemorrhage in the cord but a persistent thymus gland and marked cardiac and renal damage. The cause of death was not definitely established, though shock seems possible. The second and third patients (cases 10 and 15) appeared to be benefited by the operation, in that the subjective symptoms disappeared and a marked regression in the morbid changes in the eyegrounds and a significant fall in blood pressure occurred. The fourth and fifth patients (cases 11 and 14) did not appear to be aided. Cardiac decompensation occurred in one, and the level of the blood pressure was at times as high as before operation. The renal function and hemoglobin content steadily diminished. It was our opinion that the natural course of the disease had not been altered. The other patient died of apoplexy.

A number of our patients exhibited so-called "fixed" hypertension, that is, the blood pressure remained high and showed little variation in spite of rest and sedatives. During operation the arterial pressure of these patients fell as markedly as in those with "labile" hypertension. In all of them it remained low long after the effects ordinarily associated with a major operation had passed off. No symptoms or signs of cardiac insufficiency were present. Consequently, although morbid changes had occurred in some of the blood vessels which were examined, either enough uninjured vessels remained which could dilate, or those vessels which appeared to be injured had not lost this power. Evidence is insufficient to decide which of the two explanations is correct. It seems important to lay stress on the observations that dilatation of blood vessels sufficient to lower the arterial pressure can occur in a patient in whom organic change in the vessels was believed to fix the arterial pressure at a high level.

Summarizing the effect of section of the anterior nerve roots on the level of the arterial blood pressure in patients who have been studied for from six to twenty-nine months after operation, the following general

statement may be hazarded Group 1 Those patients in whom the disease is benign but in whom advanced vascular change has not occurred may respond well Group 2 In cases of more advanced, longstanding involvement with morbid vascular change but with a benign character a favorable result may occasionally be obtained Group 3 Young patients exhibiting symptoms and signs of the "diencephalic syndrome" may respond in a satisfactory manner Group 4 Patients suffering from highly malignant hypertension rarely respond favorably

Observation of patients following operation shows clearly that in groups 2 and 4 the arterial pressure may remain markedly reduced for periods up to six months but that a slow rise then usually occurs until the preoperative level is nearly reached The subjective improvement of most patients was so marked that they felt the operation was justified As the therapeutic effects, both subjective and objective, are more evident in groups 1 and 3, further investigations employing this or other simpler operative procedures appear warranted The tendency for the arterial pressure to return to its preoperative level has been much less definite It must be remembered, however, that the period of postoperative study has been only two and one-half years in the latter groups, hence, great caution is necessary in evaluating the effects of the operation on the natural history of the disease

The normal level of urea clearance before operation in our cases of hypertension makes it appear probable that the renal blood flow in these cases was merely normal and not elevated by the hypertension This is based on the observation of Van Slyke, Rhoads, Hiller and Alving²¹ that in dogs the urea clearance parallels chiefly the renal blood flow It appears probable that the same parallelism occurs in patients

It has been shown¹ that an abnormal elevation of the arterial pressure in cases of essential hypertension or nephritis does not appear to assist in the maintenance of renal efficiency The values for the urea clearance obtained when the blood pressure was high were compared with those obtained after the pressure was reduced entirely or partly to normal, either spontaneously or as the result of injections of sulfur, the administration of sodium thiocyanate or a major operation No fall in the clearance accompanied the observed decreases in the blood pressure Data in this paper offer additional evidence of the same nature, for a marked reduction in the arterial pressure followed the operation of section of the anterior nerve roots without significant change either in the urea clearance or in the ability to concentrate urine

Renal denervation by means of stripping the renal pedicle does not alter the urea clearance in cases of essential hypertension or nephritis,³⁰

³⁰ Page, I. H., and Heuer, G. J. The Effect of Renal Denervation on the Level of Arterial Blood Pressure and Renal Function in Essential Hypertension, *J. Clin. Investigation* **14** 27, 1935 The Effect of Renal Denervation in Patients Suffering from Nephritis, *ibid* **14** 443, 1935

and, as the kidneys are partially denervated as the result of the operation of section of the anterior nerve roots, observations on patients subjected to this operation are comparable to those following stripping of the renal pedicle. Again no change in the urea clearance was observed as a result of the denervation.

It appears that changes in the blood flow in the kidneys may occur independently of the extrinsic nerve supply.³⁰ The kidneys show a degree of vascular autonomy comparable to that of the brain. The fact that the caliber of the renal vessels may vary without assistance from the extrinsic nerve supply does not, however, prove that the nerve supply plays no part in their control.

Proteinuria and hematuria were insignificant in all the patients except two (cases 9 and 11) of those suffering from malignant hypertension. The hemoglobin value usually was temporarily reduced as a direct result of the operation, but this was soon corrected. Iron (1 Gm three times a day) has been employed to aid in its regeneration. The plasma proteins were uninfluenced by the operation.

Except for an occasional reduction in the intensity of the papilledema, the most striking change in the fundi apparently resulting from the operation was relaxation of the constricted retinal arterioles. In two patients (cases 10 and 15) absorption of the hard, white exudate was observed. Secondary glaucoma disappeared in one patient (case 19).

Changes in the size of the heart, as measured by the shadow on an x-ray plate, and changes measured on the electrocardiogram, are summarized in table 2. Preponderance of the left ventricle was present in all the patients, and the atrioventricular conduction time varied from 0.12 to 0.2 second. In two cases (cases 11 and 13) significant reduction occurred after the operation (0.2 to 0.16 second). In a few of the patients (case 1, 2, 8, 11, 12 and 13) the size of the cardiac shadow on x-ray films was slightly reduced (fig. 13), while in the remainder no significant change was observed. Alterations of the electrocardiograms were not considered significant.

Besides the fall in the arterial pressure, the disappearance in subjective symptoms was striking. This cannot confidently be attributed entirely to the effects of operation in lowering the blood pressure. Certainly a major operation in conjunction with a prolonged period of rest in bed before the operation tends to reduce emotional instability.

It was of interest to observe that the "hypertensive diencephalic syndrome" did not disappear in some of the patients. Briefly, this syndrome, as described by one of us (I. H. P.),²⁹ consists of the spontaneous appearance of a mottled blush over the face and the upper part of the chest, both front and back, sweating, lacrimation, palpitation, a

slight rise in blood pressure, occasionally increased peristalsis and primitive emotional behavior. The basal metabolism may be normal. Blushing, sweating, lachrimation and palpitation are most often observed. Similar groups of signs and symptoms may occur in patients other than those suffering from hypertension, yet its frequent occurrence in

TABLE 2—*Summary of the Electrocardiographic Changes and the Changes in the Size of the Heart as Observed Roentgenographically*

Case	Time in Relation to Operation	Time, Weeks	Electrocardiographic Changes				Time, Weeks	Transverse Diameter of Heart, Cm	Internal Diameter of Chest, Cm
			T Wave, Leads			Other Changes			
			I	II	III				
1	Before	8	+	+	±	R III split, low voltage	2	12.9	23.0
	After	88	+	+	+		84	12.4	24.0
2	Before	2	+	+	—		2	10.5	22.0
	After	64	+	+	+		40	10.2	23.5
3	Before	4	+	+	—	Q III	4	10.1	23.5
	After	60	+	+	±		60	10.6	23.8
4	Before	1	+	+	—		3	10.6	23.6
	After	60	+	+	+		44	10.6	22.7
5	Before	2	+	+	+	P III diphasic	3	12.0	25.0
	After	63	+	+	+		24	12.1	25.0
6	Before	2	+	+	—		2	14.8	26.0
	After	24	+	+	—		28	14.4	26.0
7	Before	2	+	+	+	Deep Q III	2	11.8	25.0
	After	12½	—	+	+	Deep Q III	17	11.8	26.0
8	Before	3	+	+	—		2	12.6	23.0
	After	52	+	+	—		50	11.2	24.1
9	Before	8	—	+	+	R II notched			
10	Before	2	+	+	—	High voltage Q R S Q III	2	13.1	26.0
	After	37	+	+	—		20	13.2	27.5
11	Before	2	—	—	+		2	17.2	27.4
	After	20	+	+	+		4	16.5	27.5
12	Before	2	—	±	+		3	13.7	27.0
	After	44	—	+	+		23	13.2	28.0
13	Before	1	—	+	+	P III split	1	16.2	27.5
	After	40	±	+	+		20	15.0	27.5
14	Before	2	+	—	—	Q R S split in leads II and III	2	13.2	27.7
	After	4	+	+	—				
15	Before	2	±	±	—	P III diphasic	4	13.2	29.0
	After	3	+	±	+		32	13.1	29.2
16	Before		+	+	+		3	13.7	29.8
17	Before	1	—	—	+		3	14.5	26.0
	After	8	—	—	+	P II split			
18	Before	2	—	+	+	Q R S high voltage, P III diphasic	2	13.1	25.5
	After								
19	Before	10	+	+	+		4	13.7	26.0
	After						8	14.6	26.5
20	Before	12	—	+	±	P III diphasic	4	14.0	27.0
	After	1	+	+	+		5	13.7	23.2

hypertensive patients suggests some intimate association with the mechanism of the disease. Should it be proved that the "hypertensive diencephalic syndrome" is indicative of irritation of the vegetative centers in the brain, some clue to the etiology of essential hypertension might be obtained from a closer study of it. Since it occurs in certain patients (cases 2 to 4) in characteristic form in spite of a reduction in the blood pressure, it may be concluded that elevation of the pressure does not cause it.

Of especial interest from the point of view of the mechanism of the reduction in blood pressure is case 17, since the patient of his own choice acted as a control. Laminectomy was performed, but the second stage of the operation, namely, opening the dura and severing the nerves, was refused. Because of the nature of the disease and this patient's response to it, we believed that a favorable result was to be expected from surgical treatment. A marked reduction in the blood pressure occurred for a short period after the operation, but the pressure soon rose to its original level, indeed above it. Had the shock of operation been responsible for the prolonged lowering of the blood pressure which was observed in some of the other patients, it might

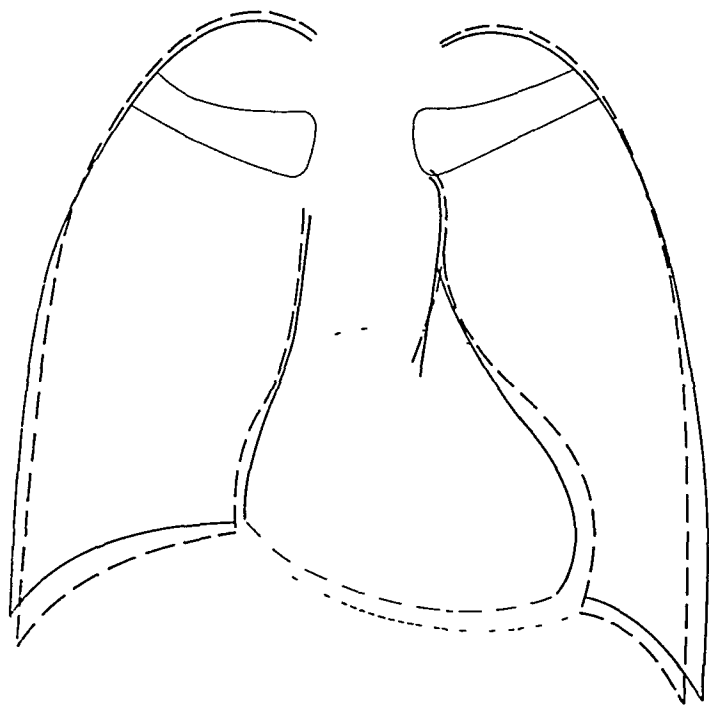


Fig 13 (case 8) —Example of a decrease in the size of the heart following operation. The broken line represents the shadow on the roentgenogram before the operation (Nov 26, 1934), and the continuous line represents the shadow seen fourteen months later (Jan 21, 1936). Planimeter measurements of the cardiac area were 102.5 sq. cm. preoperatively and 86.4 sq. cm. postoperatively.

have been anticipated that the arterial pressure in this patient also would have remained at the lower level.

In contrast to this case is case 16, in which transverse myelitis occurred at the eleventh dorsal segment. The arterial pressure was reduced and has remained at the lowered level for eight months.

Opinion differs among investigators regarding the participation of the nervous system in the genesis of the hypertonus of the blood ves-

sels responsible for hypertension. The fact that prolonged reduction of the arterial pressure occurs following section of anterior spinal nerve roots suggests that the hypertonus is at least in part due to vasoconstrictor impulses. But it does not indicate whether these impulses are increased in frequency and intensity or are normal. Since in some patients the pressure tends to return to the preoperative level after a greater or lesser period of time, it is conceivable that either an insufficient vascular bed has been denervated or, as seems more reasonable, that some peripheral mechanism functions to cause hypertonus.

Associated with the question of the return of the blood pressure to its preoperative level is the problem of regeneration of the nerve roots. Although regeneration of the nerve ends after severance between silk ties might seem improbable, nevertheless it is a possibility. That it did not occur within a period of ten and seventeen months, respectively, is proved by case 11 and case 13. Careful examination of the cord at autopsy failed to show any regeneration.

Adson and Brown,²⁰ the originators of this operation, have published their results obtained in twenty-seven cases in preliminary form and one case in detail. The longest period of observation after operation was five years. The patient was a man with malignant hypertension. The blood pressure fell markedly and remained at levels from 140 to 166 mm of mercury systolic and 80 to 110 mm diastolic for a year and a half. Postoperative bleeding developed, which necessitated opening the wound. This was followed by weakness of the legs. Brown, Craig and Adson reported³¹ that their studies were carried out from three to six weeks after operation. The mean values for the systolic pressure were 44 mm systolic and 38 mm diastolic less than before operation. The average reduction in the cold-pressor response (Hines-Brown test) was 80 mm systolic and 45 mm diastolic. When the patient was recumbent the arterial pressure was higher than when he was upright. Definite relaxation of the retinal arterioles occurred in some cases. Regression of retinitis was noted two or three weeks after the operation. Pain in the legs, which persisted for two weeks or more after the operation, was complained of by three patients. There was usually some subjective hyperesthesia of the skin of the thighs. A diminution in the transverse diameter of the heart was demonstrated after the operation in two cases.

Brown, Craig and Adson made the following statement: "Subjects less than 50 years of age, who have a relatively short history of hypertension, who present a serious prognosis, who have adequate function

31 Brown, G. E., Craig, W. McK., and Adson, A. W. The Treatment of Severe Essential Hypertension. Effects of Surgical Procedures Applied to the Sympathetic Nervous System, *Minnesota Med* 18 134, 1935.

of the kidneys, and in whose blood pressure reactions there is a large spastic element, as demonstrated by the excessive response to cold, and to emotional and other stimuli, are primary requisites" in the selection of patients for operation. These careful observers stated with wise judgment that "the ultimate value of this operation on the course and progression of these serious types of hypertension is not known."

Our experience confirms to a large extent that of Adson, Craig and Brown³². Although in some cases the arterial pressure has risen after a period of months to higher levels it has not returned to the pre-operative level. In those cases in which the average arterial pressure was not greatly lowered as the result of the operation there was a return to the preoperative level within a few weeks. None of our patients complained of pain in the legs following the operation. We agree with Brown, Adson and Craig that it is too early to be certain of the ultimate effect this operation will have on the natural course of the disease. It is our opinion that some of the patients have markedly benefited both subjectively and objectively (in two and one-half years), even though perhaps temporarily, that others have been benefited subjectively and that others have received no benefit but have not been harmed by the operation. We do not regard the operation as an established therapeutic procedure even in those cases in which the benefits have been most marked. Disability resulting from the operation has not been observed in any of the patients except when complications have been encountered.

Since the operation is a major surgical procedure with a number of inherent risks, the results must be judged most critically for a relatively small number of patients before there can be any justification of its employment for large numbers of patients. It was with this purpose in mind that the present investigation was undertaken.

SUMMARY

Evidence of varied nature indicates that, as part of a more generalized vasoconstriction, vessels of the splanchnic area are narrowed in patients suffering from essential or malignant hypertension. Since no contraindications are known for reduction of the arterial pressure in such patients and there is no known medical treatment of more than temporary value, it appears to be justified to attempt to abolish the extrinsic vasomotor control of this area by section of the anterior nerve roots with the hope of reducing the arterial pressure. It has seemed desirable also to learn more of the part played by the nervous

32 Adson, A. W., Craig, W. M., and Brown, G. E. *Surgery in Its Relation to Hypertension*, Surg., Gynec. & Obst. **62**: 314, 1936.

system in the genesis of hypertension To this end seventeen patients have been subjected to the operation of section of the anterior nerve roots

No attempt was made to select patients in whom in our opinion a favorable outcome might be anticipated Six patients showed benign involvement of long duration, three of them with moderate vascular changes and three with severe changes Six were young women with signs and symptoms of the "hypertensive diencephalic syndrome" Five suffered from highly malignant hypertension The results of operation are therefore not comparable except within the subgroups

While the ultimate effect of this operation on the natural course of hypertension cannot be foretold, from a study of these patients for periods of from eight to thirty-seven months after operation, the following results may be listed (a) Three patients in whom the disease was severe but still benign and without advanced vascular change responded well (b) One of three patients with more advanced involvement of long standing, with marked sclerotic but benign vascular changes, responded favorably The headaches were relieved in the second and third cases, but the progress of the disease was unchecked (c) Six young patients exhibiting the "hypertensive diencephalic syndrome" appeared benefited (d) Three of those suffering from highly malignant hypertension were unaided by the operation, and two appeared to be improved The favorable responses have been a marked, prolonged lowering of the arterial pressure, the remission of such symptoms as headache, pressure in the head and easy fatigability and marked improvement in the disposition Other evidence of improvement in some of the patients has been relaxation of the spasm of the arterioles in the retina (eleven cases), absorption of exudate (two cases), disappearance of papilledema (three cases) and secondary glaucoma (one case), slight reduction in the size of the cardiac shadow in the roentgenograms (eight cases) and reversal of the T wave from the inverted to the upright position in lead I (two cases) There has been a definite tendency for a slow rise in pressure to occur over a period of two and one-half years in most but not all patients Judgment must therefore be reserved as to the ultimate effects of the operation on the natural history of the disease

Although marked anatomic change was present in the vessels of some of the patients, this did not prevent a marked fall in the arterial pressure, which persisted long after the patient had recovered from the immediate effects of the operation This demonstrates that anatomic changes in the vessels do not account for the persistence of hypertension

Renal efficiency, as measured by the urea clearance and the ability to concentrate urine, was unchanged either by the partial denervation of the kidneys which resulted from the operation or from the fall in blood pressure

In those patients exhibiting the "hypertensive diencephalic syndrome" a marked lowering of the blood pressure did not cause it to disappear. If this syndrome is the somatic expression of irritation of vegetative centers in the brain stem and is not abolished by a reduction of the arterial pressure, it is probably not caused by elevation of the arterial pressure

The operation of laminectomy does not of itself reduce the arterial pressure for more than several weeks. Transverse myelitis at the eleventh thoracic segment reduces it for prolonged periods (one patient was studied for nine months). These observations, with those concerning the effect of section of the anterior spinal nerve roots on the arterial blood pressure, suggest that the nervous system plays some part in the genesis of hypertension

Although the operation has markedly improved the clinical condition of many of the patients studied for periods up to two and one-half years, its ultimate value in the *treatment* of hypertension has not been established

RECKLINGHAUSEN'S NEUROFIBROMATOSIS

CLINICAL MANIFESTATIONS IN THIRTY-ONE CASES

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OMAHA

In a study of Recklinghausen's neurofibromatosis, a system disease, one is immediately impressed with (1) the lack of a known etiologic factor, (2) the apparent widespread differences of the various clinical types and (3) the lack of any known beneficial treatment. Though a great number of isolated cases have been reported,¹ there has been com-

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1 Weber, F Parkes, and Boch, O B Recklinghausen's Neurofibromatosis with Unilateral Buphthalmus and Multiple Changes in the Face and Skull, Proc Roy Soc Med **27** 638-640 (April) 1934 Marshall, W, and Watt, A W A Case of von Recklinghausen's Disease, with Note on Psychology, Brit M J **1** 234-235 (Feb 10) 1934 Sykes, E M Neurofibroma of Orbit of von Recklinghausen's Disease, Texas State J Med **29** 447-449 (Nov) 1933 Sanford, J A, and Thomas, E P Von Recklinghausen's Disease with Unusual Distribution of Neoplastic Nodules, South M J **26** 892-894 (Oct) 1933 Lentaker, R J, and Ward, J H Neurofibromatosis with Report of a Case, U S Nav M Bull **31** 301-305 (July) 1933 Hankey, G T Von Recklinghausen's Disease with Local Tumor of the Palate Proc Roy Soc Med **26** 959-961 (June) 1933 Wayson, J T Multiple Fibromas Recklinghausen's Disease, Arch Dermat & Syph **27** 421-423 (March) 1933 Amerod, F C Bilateral Auditory Nerve Tumor in a Case of Multiple Neurofibromatosis Case, Proc Roy Soc Med **26** 566-567 (March) 1933 Knapp, A A Von Recklinghausen's Disease Case Presenting Involvement of the Left Eyelids, J A M A **100** 494-495 (Feb 18) 1933, Multiple Neurofibromata of Acoustic Nerve, Brain and Spinal Cord (Cabot Case), New England J Med **208** 849-851 (April 20) 1933 Else, J E Von Recklinghausen's Disease, with Tumor of the Spinal Cord, S Clin North America **13** 25-27 (Feb) 1933 Kass, I H Neurofibromatosis of the Bladder, Am J Dis Child **44** 1040-1047 (Nov) 1932 Lightwood, R Naevo Neurofibromatosis, Proc Roy Soc Med **25** 1738 (Oct) 1932 Corsi, H A Rare Type of von Recklinghausen's Disease, *ibid* **25** 1739 (Oct) 1932 Scarff, J W Case of von Recklinghausen's Disease, M Clin North America **15** 1267-1273 (March) 1932 Goldstein, I, and Wexler, D Spongioneuroblastoma of Optic Nerve in Neurofibromatosis (Recklinghausen), Arch Ophth **7** 259-267 (Feb) 1932 Diaso, F A Elephantiasis Neuromatosis Case, Urol & Cutan Rev **36** 104-107 (Feb) 1932 Telford, E D, and Stapford, J S B Arterial Thrombosis Associated with Neurofibromatosis of Lumbar Sympathetic Cord, Lancet **2** 16-17 (July 4) 1931 Moore, R F Diffuse Neurofibromatosis with Proptosis, Brit J Ophth

(Footnote continued on next page)

paratively little attempt to weave together the many loose threads of this clinicopathologic syndrome. During the past three years thirty-one patients with Recklinghausen's neurofibromatosis have been observed. In this report it is proposed to demonstrate examples of the multiple manifestations of the condition and to emphasize the influence of various physiologic factors and life experiences on the disease.

ETIOLOGY

Though many theories have been advanced, the cause of Recklinghausen's neurofibromatosis is unknown. The disease is not limited to

15 272-279 (May) 1931 Phelan, H V Multiple Neurofibromas of Nasociliary Nerve, *Arch Ophth* **5** 800-802 (May) 1931 Anzinger, F P Congenital Plexiform Neurofibromas and Elephantiasis Neuromatosa of the Right Arm and Neck (von Recklinghausen's Disease), *J A M A* **96** 1381-1382 (April 25) 1931 Smith, F R Neurofibroma of Ovary Associated with von Recklinghausen's Disease, *Am J Cancer* **15** 859-862 (April) 1931 Beatty, N M, and Gregor, F W Neurofibromatosis, Familial, with Unusual Manifestations, *J Indiana M A* **24** 72-76 (Feb) 1931 Russum, B C, and Barry, M W Paraganglioma in Suprarenal Medulla with Neurofibromatosis, *Nebraska M J* **15** 243-244 (June) 1930 Goldstein, I, and Wexler, D Melanosis Uvae and Melanoma of the Iris in Neurofibromatosis, *Arch Ophth* **3** 288-296 (March) 1930 Callender, G R, and Thigpen, C A Two Neurofibromas in One Eye, *Am J Ophth* **13** 121-124 (Feb) 1930 Sachs, E Multiple Neurofibromatosis (von Recklinghausen's Disease) Affecting Posterior Root of Cervical Nerve with Pressure on the Spinal Cord, *J Missouri M A* **26** 180-192 (April) 1929 Rogers, L Macrodactylia in Child Due to Neurofibromatosis (Elephantiasis Neuromatosa), *Brit J Surg* **16** 684-686 (April) 1929 Pack, G T Unilateral Neurofibromatosis of Cranial and Deep Cervical Nerves Report of a Case, *Arch Neurol & Psychiat* **21** 919-923 (April) 1929 Spittal, R L, and Fernando, S E Elephantiasis Neuromatosa Case Report, *Brit M J* **1** 596-597 (March 20) 1929 Hine, M L, and Wyatt, R B H Neurofibromatosis of Right Orbit Case, *Brit J Ophth* **12** 513-518 (Oct) 1928 Hoey, T Von Recklinghausen's Disease Associated with Fibroma of the Appendix, *Brit M J* **2** 490 (Sept 15) 1928 Eller, J J Incomplete Form of von Recklinghausen's Disease Report of Cases, *Arch Dermat & Syph* **17** 648-649 (May) 1928 Goodwin, W H Von Recklinghausen's Neurofibromatosis with Report of Cases, *Virginia M Monthly* **55** 79-88 (May) 1928 Robinson, J H Neurofibromatosis Report of Two Cases, *Lancet* **2** 1074 (Nov 19) 1927 Bridgeman, M L Von Recklinghausen's Disease, or Neurofibromatosis, *Northwest Med* **25** 144-145 (March) 1926 Wiener, A Case of Neurofibromatosis with Buphthalmus, *Arch Ophth* **54** 481-488 (Sept) 1925 Fleming, G W T H, and Cookson, H A Case of Multiple Neurofibromata Associated with True Angioneurofibroma of Acoustic Nerve, Jacksonian Epilepsy and Osteoporosis, *J Neurol & Psychopath* **6** 104-113 (Aug) 1925 Shouldice, E Neurofibromatosis Case with One Fibroma Enlargement into Stomach, *Canad M A J* **15** 66-69 (Jan) 1925 Parker, H L A Case of von Recklinghausen's Disease with Involvement of Peripheral Nerves, Optic Nerve and Spinal Cord, *J Nerv & Ment Dis* **56** 441-452 (Nov) 1922 Elliott, C A, and Beifeld, A F Generalized Neurofibromatosis (von Recklinghausen's Disease) Report of a Case Showing a Superficial Resemblance to Hodgkin's Disease, *J A M A* **63** 1358-1362 (Oct 17) 1914

the white population but has been reported in the black, red and yellow races also. It is said to be slightly more common among males. In many cases it is almost impossible to determine the age of the patient at the time of the onset of the disease. Though cutaneous pigmentation and tumors may be present at birth, it seems more common for the pigmentation to develop during early infancy, with the insidious appearance of the tumors in later life. As Thomson² has pointed out, it is reasonable to assume that the disease has existed long before it can be recognized. This fact is especially true when one considers the distinct hereditary tendency of the disease. Though it was long suspected, it was not until 1915 that Preiser and Davenport³ in a study of one hundred and fifteen offspring of twenty patients found that 43.5 per cent of the offspring were affected. This at once suggested that the hereditary factor in neurofibromatosis is a dominant one. They found that the disease tends to recur without a break in several generations, with little or no difference in the distribution as regard to the sex of the parent who transmitted the disease. In addition, there seems to be a definite familial resemblance as to the type and location of the principal tumors, the tendency to produce similar pigmentation, the tendency to produce confluent tumors (elephantiasis) and, finally, the tendency for sarcomas to develop. This familial resemblance of the distribution of the tumors is strikingly exemplified in Gardner and Frazier's⁴ report of a family in which there were thirty-eight persons with deafness due to bilateral acoustic neurofibromas, fifteen of whom subsequently became blind. Various associated congenital and developmental anomalies, such as cerebral meningocele, spina bifida, cranial defects and defects of the fingers and toes, are found with significant frequency.⁵ There are occasional cases in which there is no apparent familial or hereditary history.

Intoxication, infection, mental distress and various external factors, such as exposure to cold, irritation and trauma, have all been suggested as possible causes of the disease. It seems more probable that their influence, if any, is that of stimulation or aggravation.⁶ Such a stimu-

2 Thomson, Alexis. On Neuroma and Neurofibromatosis, Edinburgh, Turnbull and Spears, 1900.

3 Preiser, S. A., and Davenport, C. B. Multiple Neurofibromatosis (von Recklinghausen's Disease) and Its Inheritance, with Description of a Case, *Am J M Sc* **156** 507-540 (Oct.) 1918.

4 Gardner, W. J., and Frazier, C. H. Bilateral Acoustic Neurofibromas, *Arch Neurol & Psychiat* **23** 266-302 (Feb.) 1930.

5 Knapp, A. A. Von Recklinghausen's Disease, *M Rec* **139** 62-64 (Jan 17) 1934.

6 Penfield, W., and Young, A. W. Nature of von Recklinghausen's Disease and Tumors Associated with It, *Arch Neurol & Psychiat* **23** 320-344 (Feb.) 1930.

lative action on the course of the disease has been frequently observed in puberty, pregnancy and the menopause⁷

In attempting to find an explanation of the syndrome known as Recklinghausen's neurofibromatosis, it is only natural that certain observers have turned their attention to a possible endocrinopathy⁸. The multiplicity of the various manifestations, the pigmentation of the skin and the osseous involvement all favor such a relationship. In addition, a number of cases have been reported in which there was associated acromegaly and various other endocrine dysfunction. Furthermore, the detrimental effect on Recklinghausen's neurofibromatosis of such physiologic factors as puberty, menstruation, pregnancy and the menopause seem to point toward an endocrine influence. Though early French and Italian authors endeavored to establish such a connection between Recklinghausen's disease and glandular dysfunction, this hypothesis has only recently been mentioned in the English literature. Levin,⁹ in summarizing the different endocrine syndromes that were associated with Recklinghausen's disease before 1921, included menstrual anomalies, incomplete and delayed sexual development, acromegaly, cretinism, myxedema, tetany and Addison's syndrome. He gave as his conclusion that the endocrine system, especially the adrenal glands, play the major rôle in the causation of neurofibromatosis. His review of the necropsy examinations of the involved endocrine glands is interesting and suggestive but is far from conclusive. Tucker,¹⁰ impressed with the endocrine relationship, especially in regard to the pituitary gland, found acromegaloid manifestations in three of nine cases, while in two additional cases a large sella was noted on roentgen examination. Barber and Shaw¹¹ reported two cases of Recklinghausen's disease associated with pituitary tumors. It is of interest that Marie,¹² in his treatise on acromegaly published in 1891, included cutaneous tumors

7 (a) Harbitz, F. Multiple Neurofibromatosis, *Arch Int Med* **3** 32-65 (Feb.) 1909. (b) Weber, F. Parkes. Periosteal Neurofibromatosis with a Short Consideration of the Whole Subject, *Quart J Med* **23** 151-155 (Jan.) 1930. (c) Noyes, A. W. F. Histopathology of Mollusum Fibrosum, *J Path & Bact* **9** 240-245, 1904. (d) Ward, E. Multiple Pigmented Warts in Pregnancy, *Brit J Dermat* **25** 153-154 (April) 1913. Thomson². Preiser and Davenport³.

8 (a) Phillips, H. T. Von Recklinghausen's Disease. Often a Difficult Surgical Problem, *South M J* **27** 212-215 (March) 1934. (b) Goodhart, S. P. Neurofibromatosis (von Recklinghausen's Disease), in Tice, F. *Practice of Medicine*, Hagerstown, Md, W. F. Prior Company, Inc., 1923, vol. 10, pp. 665-667.

9 Levin, O. L. Recklinghausen's Disease. Its Relation to the Endocrine System, *Arch Dermat & Syph* **4** 303-321 (Sept.) 1921.

10 Tucker, Beverly. Von Recklinghausen's Disease, with Special Reference to the Endocrine System, *Arch Neurol & Psychiat* **11** 308-320 (March) 1924.

11 Barber, H. W., and Shaw, M. *Brit J Dermat* **34** 207-208 (Feb.) 1922.

12 Marie, P., and Suoza-Leite. *Essays on Acromegaly*, London, Adlard & Son, 1891.

of the face and neck, which he termed molluscum fibrosum, as a part of the characteristic findings of the disease. However, Atkinson¹³ in a recent study of seven hundred and sixty-eight reports of cases of acromegaly collected from the literature, found Recklinghausen's disease present in only four cases.

In contradistinction to the endocrine theory of the primary cause of Recklinghausen's neurofibromatosis, Clark and Wakefield¹⁴ suggested the possibility that involvement of the endocrine system is a secondary complication of the disease and that the primary pathologic involvement is sympathetic or parasympathetic or both. Schneiderman¹⁵ and Weber^{7b} stated that since all other organs may be involved in the disease, so may the endocrine glands. Gordon¹⁶ had a patient with an acromegaloid appearance who showed a normal sella and pituitary gland, while Gould¹⁷ had the opportunity of studying several cases in which there were changes of the osteomalacic type and observed no postmortem changes in either the pituitary gland or the parathyroid glands. Gordon,¹⁸ in analyzing the literature, stated the conclusion that nothing definite has been advanced to prove that the endocrine glands act in themselves as an etiologic factor but that a common genetic factor is responsible for both sets of symptoms. What little organotherapy has been tried in this disease has had little or no effect on the cutaneous manifestations.¹⁹

The theory of a congenital embryonal disturbance has often been advanced as a possible explanation of neurofibromatosis. Pende²⁰ said he believed that two factors are necessary for the production of the disease: (1) a hereditary constitutional factor, represented by an abnormal endocrine-sympathetic system, and (2) an accidental factor, such as shock, trauma, toxic poison or infection, which, through its effect on the endocrine-sympathetic system, acts as a stimulus to the embryonal elements. Schneiderman¹⁵ suggested that there is "a physical, chemical

13 Atkinson, F. R. B. *Acromegaly*, London, John Bale, Sons & Danielsson, Ltd., 1932.

14 Clark, G. F., and Wakefield, E. G. Cardiovascular Disease as a Complication of Generalized Neurofibromatosis, *Arch. Dermat. & Syph.* **13**: 806-814 (June) 1926.

15 Schneiderman, H. Recklinghausen's Disease, *Arch. Dermat. & Syph.* **12**: 483-491 (Oct.) 1925.

16 Gordon, S. Hemorrhage as a Complication of von Recklinghausen's Disease, *Canad. M. A. J.* **27**: 524-525 (Nov.) 1932.

17 Gould, E. P. Bone Changes Occurring in von Recklinghausen's Disease, *Quart. J. Med.* **11**: 221-227 (April) 1918.

18 Gordon, M. B. Endocrine Consideration. Report of a Case with Associated Childhood Myxedema, *Endocrinology* **13**: 553-563 (Nov.-Dec.) 1929.

19 Gordon¹⁸ Levin⁹ Knapp⁵

20 Pende, cited by Levin⁹ Muto, A. *Riv. di pat. nerv.* **15**: 656-670, 1910.

on nutritional disturbance in the environment of the developing embryo at the stage when the ectoderm is forming the nervous system" and that this defect is "transmitted to the following generations according to the mendelian law" Ewing²¹ expressed the belief that the underlying factor is a disturbance in the relations between the fetal ectoderm and the tissues which it innervates, while Miller²² supported the hypothesis that neurofibromatosis is a manifestation of a congenital disturbance of the mesenchyme Yakovlev and Guthrie²³ and more recently Schwarz and Abramson²⁴ agreed that the disease is probably due to a congenital maldevelopment of organs of ectodermal derivation but added to neurofibromatosis both tuberous sclerosis and angiomatosis of the brain, with nevi of the skin in the trigeminal area, as additional overlapping and parallel congenital malformations These they classed as congenital ectodermoses (neurocutaneous syndromes)

CLINICAL TYPES

There is considerable difficulty in attempting to define and differentiate the various clinical types of Recklinghausen's neurofibromatosis With such widespread lesions affecting almost any part of the body and more especially the skin and nervous system, no two cases are similar The term neurofibromatosis is misleading in that it lays undue emphasis on only one part of the clinical manifestations, viz, the cutaneous and subcutaneous tumors Though this is a common part of the syndrome, it is usually present in the cases of more advanced and complete involvement Pigmentation of the skin, osseous changes and elephantiasic thickenings of soft tissues, alone or in combination, also are to be considered characteristic features of the disease The term Recklinghausen's disease has been suggested as a more inclusive term than neurofibromatosis

Incomplete Form—The irregular patches of yellowish brown café au lait pigmentation may be the only manifestation of the disease²⁵

21 Ewing, James Neoplastic Diseases, Philadelphia, W B Saunders Company, 1922, pp 152-154

22 Miller, Alexander Neurofibromatosis with Reference to Skeletal Changes, Compression, Myelitis and Malignant Degeneration, Arch Surg **32** 109-122 (Jan) 1936

23 Yakovlev, P I, and Guthrie, R H Congenital Ectodermoses (Neurocutaneous Syndromes) in Epileptic Patients, Arch Neurol & Psychiat **26** 1145-1194 (Dec) 1931

24 Schwarz, H, and Abramson, H Neurocutaneous Syndromes in Childhood, J Pediat **3** 586-607 (Oct) 1933

25 (a) Leader, S D, and Grand, M J H Von Recklinghausen's Disease in Children Report of a Case Presenting Cutaneous Pigmentation and Bone

This monosymptomatic form, the so-called incomplete type, or forme fruste, is usually found in a child with a parent or some other relative who has the complete form of the disease. The pigmentation is thought to be due to fibromatosis of the terminal filaments of the cutaneous nerves.²² The pigmentation, which is usually confined to the trunk and unexposed surfaces, may precede by years the formation and appearance of the characteristic cutaneous and subcutaneous nodules. It is rarely symmetrical and does not follow the distribution of any particular nerve or nerves.² The spots and patches of pigmentation usually increase in number and size with advancing years. Pigmentation is said to be present in only 25 per cent of the cases,²⁶ but from our experience and from a survey of the literature it seems that it is present in a much higher percentage of cases.

Neurofibromatosis—The general character of the cutaneous and subcutaneous tumors of Recklinghausen's disease are too well known to need further description. Their variability in location, distribution and size is well appreciated. They may occur in the skin or subcutaneous tissues, the deep or superficial nerves, the sympathetic or parasympathetic nerves or the cranial or spinal nerves. They may be small or large, localized or diffuse, single or multiple. Although they are usually painless, they may cause pain through pressure on or involvement of the nerve roots. The size and number of the tumors may be progressive or may remain stationary. The growths rarely regress in size. They are most commonly found on the trunk and are usually associated with cutaneous pigmentation. When the lesions are confined to the skin the condition is termed molluscum fibrosum, but Weber^{7b} warned that the presence of one or two small tumors is not at all rare in an otherwise normal subject. If the neurofibroma is confined to the distribution of one or more contiguous nerves or a plexus of nerves, the term plexiform neurofibroma has been applied.

Osseous Changes—At first considered an accidental association, skeletal deformity has now come to be regarded as an important and characteristic part of Recklinghausen's disease.²⁷ This is not to be

Changes, *J Pediat* **1** 754-763 (Dec.) 1933. (b) Wise, F., and Eller, J. J. Von Recklinghausen's Disease Without Tumor Formation. Incomplete or Abortive Forms of the Disease, *J A M A* **86** 86-90 (Jan. 9) 1926. (c) Weber, F. Parkes. Cutaneous Pigmentation as an Incomplete Form of von Recklinghausen's Disease, with Remarks on the Classification of Incomplete and Anomalous Forms of von Recklinghausen's Disease, *Brit J Dermat* **21** 49-53 (Jan.) 1909. Goodhart^{8b}

²⁶ Thomson² Harbitz^{7a} Knapp⁵

²⁷ Stewart, C. C. Neurofibromatosis in Children. Report of Two Cases, *New England J Med* **210** 150-152 (Jan. 18) 1934. Copeland, M. M., Craver, L. F., and Reese, A. B. Neurofibromatosis with Ocular Changes and Involvement of the Thoracic Spine, *Arch Surg* **29** 108-112 (July) 1934. Miller²²

confused with Recklinghausen's hyperparathyroidism. In 1921 Weiss²⁸ called attention to the presence of scoliosis in fifteen cases of neurofibromatosis, but it remained for Brooks and Lehman²⁹ to describe and classify the various types of osseous changes present in their seven cases. These included (1) scoliosis, by far the most common, (2) abnormalities of growth, most commonly associated with elephantiasis, and (3) subperiosteal cysts. All the osseous changes have been explained by involvement of the bone by growth of the tumor. The deformity may be noted first in early childhood. Weber^{7b} has recently substantiated this explanation. Gould¹⁷ mentioned a fourth type of osseous change in describing findings similar to osteomalacia. Lehman³⁰ in a later paper again stressed the osseous changes as being of great diagnostic importance and added the cystic areas in the skull, detected only by complete roentgenographic examination. Pigmentation of the skin and osseous changes may occur in the absence of palpable or visible neurofibromatosis³¹. Twenty-three per cent of all the tumors of the spinal cord are neurofibromas, and a competent roentgenologist can directly localize the lesion in 42 per cent of the cases through alterations in the structure of the vertebrae and adjoining ribs and soft tissues³². Erosion of vertebral bone with compression myelitis has occurred²². It is emphasized that a complete roentgenographic examination should be made in all cases of Recklinghausen's disease.

Elephantiasis Neuromatosa—This form of Recklinghausen's neurofibromatosis usually occurs as a part of the more advanced stage of the disease and in general consists of a prominent diffuse overgrowth of the skin and subcutaneous tissue of the head, neck, trunk or extremity. More than one third of the elephantiasic overgrowths originate in the temporal region. They are more common in men³³ and are nearly always unilateral^{7b}. They may result, either singly or in combination with general cutaneous manifestations, from a large molluscum fibrosum.

28 Weiss, R. S. Von Recklinghausen's Disease in the Negro. Curvature of Spine in von Recklinghausen's Disease, *Arch Dermat & Syph* **3** 144-151 (Feb) 1921.

29 Brooks, B., and Lehman, E. P. Bone Changes in von Recklinghausen's Neurofibromatosis, *Surg., Gynec & Obst* **38** 587-595 (May) 1924.

30 Lehman, E. P. Recklinghausen's Neurofibromatosis and the Skeleton. A Plea for Complete Study of the Disease, *Arch Dermat & Syph* **14** 178-187 (Aug) 1926.

31 Schwarz and Abramson²⁴. Leader and Grand^{25a}.

32 Camy, J. D. A Roentgenologic Study of Osseous Changes with Neurofibromatosis of the Spinal Cord and Associated Nerves, *Proc Staff Meet., Mayo Clin* **8** 329-341 (April 19) 1933.

33 Helmholz, H. F., and Cushing, Harvey. Elephantiasis Nervorum. A Manifestation of von Recklinghausen's Disease, *Am J M Sc* **132** 355-378 (Sept) 1906.

or from a plexiform neurofibroma.² The tumor is often unsightly and horribly disfiguring and with an increase in size becomes pedunculated or pendulous. The tumor may be either a lobular or a diffuse overgrowth. The overlying skin is usually pigmented and may be either smooth or, more commonly, hard and uneven.

In addition to these four loosely knit and overlapping types of Recklinghausen's disease, there are other clinical manifestations that have been reported in the literature with such significant regularity that they too must be included as a minor part of the symptom complex.

Deafness—Neuroma of the acoustic nerve is most commonly single and constitutes 73 per cent of all verified tumors of the brain.³⁴ A high percentage of the more rare bilateral tumors of the acoustic nerve are associated with Recklinghausen's disease.³⁵ They originate in the vestibular portion of the eighth nerve. In 1930 Gardner and Frazier⁴ found that a total of thirty-seven cases had been reported in which such a tumor was associated with neurofibromatosis and seven others in which it was apparently unassociated with other evidence of the disease. The deafness may begin on one side, the usual age at onset varying from 20 to 35 years. Progressive bilateral nerve deafness, progressive recession of vision, with choked disk, and other late signs of increasing intracranial pressure are the usual procession of events unless an early diagnosis is made and neurosurgical intervention is carried out.

Mental Defect—Imbecility, mental aberration and psychic disturbances are integral parts of the complete picture of the disease.³⁶ Leader and Grand^{25a} stated as their opinion that it is a result of an endocrine influence and that mental deficiency is not a common finding. However, Charpentier³⁷ found that 63 per cent of his patients showed mild psychic defects, with a tendency to depression. Preiser and Davenport³ found that 78 per cent of two hundred and forty-three patients were feeble-minded (twenty times more than in the average population). Yakovlev and Guthrie²³ gave as their opinion that congenital anomalies of the skin are relatively more common among epileptic patients than among persons with other illnesses or among normal persons.

34 Cushing, Harvey. Tumors of the Nervus Acusticus, Philadelphia, W. B. Saunders Company, 1917, pp. 148 and 210.

35 (a) Symonds, C. D. Bilateral Eighth Nerve Tumors Associated with Multiple Neurofibromatosis, *J. Neurol. & Psychopath.* **2** 143-153 (Aug.) 1921.
(b) Jacobsen, V. C. Fibroma of the Acoustic Nerve, *Am. J. Path.* **1** 259-272 (May) 1927.

36 Gordon¹⁸ Yakovlev and Guthrie²³

37 Charpentier, quoted by Bassoe, P., and Nuzum, F. Report of a Case of Central and Peripheral Neurofibromatosis, *J. Nerv. & Ment. Dis.* **42** 785-796 (Dec.) 1915.

PATHOLOGIC PICTURE

Since von Recklinghausen³⁸ originally described the tumors as originating in the connective tissue (1882), controversy has centered about their development from mesodermal or ectodermal tissue^{39b}. The result has been the use of such terms as multiple neuroma, peripheral glioma, schwannoma, perineurial fibroblastoma and multiple neurinoma in the pathologic description.

In Virchow's³⁹ description the tumors of this disorder were classed as false neuromas because of the lack of nerve cells. Thomson² in his description subdivided Virchow's classification into solitary and multiple false neuromas. In more recent years the tumors of the nerve sheaths have been said by Verocay,⁴⁰ Masson⁴¹ and others to arise from cells of the sheath of Schwann and to be ectodermal in origin. Penfield,⁴² on the basis of his own exhaustive studies and the work of Mallory,⁴³ Rhoads and Van Wagenen,⁴⁴ stated the belief that the tumors of the nerve sheath are due to a reaction of the connective tissue. Because the outstanding histologic characteristics are suggestive of such a reaction, he referred to the solitary tumor of the nerve sheath of the same type as a perineurial fibroblastoma and retained the common term for the multiple tumors—the neurofibroma of Recklinghausen's disease. Penfield^{42a} has stated that the two types of tumor may be differentiated. The presence of nerve fibers in the tumors show that one is dealing with a neurofibroma and not a perineurial fibroblastoma. In the latter the nerve fibers of the parent nerve will be found about the tumor in the capsule, not entering the tumor.

Histologically the neurofibromas of Recklinghausen show considerable variation. There is no typical pattern, as is the case in fibro-

38 von Recklinghausen, F. Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen, Festschrift, Rudolf Virchow, Berlin, A. Hirschwald, 1882.

39 Virchow, R. Die krankhaften Geschwulste, Berlin, A. Hirschwald, 1863, p. 3.

40 Verocay, J. Zur Kenntnis der "Neurofibrome," Beitr. z. path. Anat. u. z. allg. Path. **48** 1, 1910.

41 Masson, P. Recklinghausen's Neurofibromatosis, Sensory Neuromas and Motor Neuromas, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, pp. 793-802.

42 Penfield, Wilder. (a) Tumors of the Sheaths of the Nervous System, Arch. Neurol. & Psychiat. **27** 1298-1309 (June) 1932, (b) Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, sect. 19. Penfield and Young.⁶

43 Mallory, F. B. The Type of Cell of the So-Called Dural Endothelioma, J. M. Research **41** 349, 1920.

44 Rhoads, C. P., and Van Wagenen, W. P. Observations on the Histology of the Tumors of the Nervus Acusticus, Am. J. Path. **4** 145-152, 1928.

blastomas, but rather a bizarre intermixture of the tumor fibers. Occasionally areas are seen where there is a palisade arrangement, with the nuclei in long rows, a characteristic feature of the perineurial fibroblastoma. Penfield^{42b} remarked that the appearance of perineurial fibroblastic growth within the tumor is doubtless due to some type of irritation of the perineurial connective tissue.

The variation in the pathologic picture has been remarkable in isolated cases. Kernohan and Parker⁴⁵ reported a most striking case of neurofibromatosis in which postmortem examination showed associated multiple meningioma and perineurial fibroblastoma. The meningeal tumors showed all stages of activity from those almost entirely made of psammoma bodies to those with hyperchromatic and giant nuclei as well as mitotic figures. A somewhat similar case with associated gliomas has been reported by Penfield^{42a} and Young.

Another interesting chapter in the pathology of Recklinghausen's disease is that of sarcomatous change or malignant transformation. The literature on this subject has been covered by Hosoi⁴⁶ in his report of two cases of multiple neurofibromatosis in which malignant transformation developed. He stated the belief that this sarcomatous development bears further evidence of the mesodermal origin of the neurofibroma. In a résumé Hosoi stated that malignant transformation takes place in about 13 per cent of all cases of Recklinghausen's disease. With the development of sarcomatous changes there is metastasis in 22 per cent. It is rare for malignant changes to develop in more than two isolated tumors, although recently Miller²² described a case in which malignant degeneration of varying degree was present in almost all the seven larger tumors studied. He expressed the belief that the sarcomatous degeneration took place simultaneously in the several neurofibromas rather than that the changes were metastatic.

PROGNOSIS AND TREATMENT

Haibitz^{7a} stated "The patients die with the disease and not from it." Extensive neurofibromatosis may be unattended by any symptoms, and unless there is visible or palpable evidence of the disease, it may remain unsuspected and unrecognized until discovered at postmortem examination. From the standpoint of clinical evolution, Schuhman and Terris discriminated (1) a stationary form, (2) a subacute form, with exacerbations and remissions of the growth of tumors, (3) an acute form, with a rapid and striking development of generalized neurofibromatosis, and (4) a malignant form, with sarcomatous degeneration of the tumors and metastasis. Though for the most part the disease

45 Kernohan and Parker, cited by Mallory⁴³

46 Hosoi, cited by Rhoads and Van Wagenen⁴⁴

may be harmless, with advancing years various serious complications may occur and alter the otherwise innocent course of the disease. It should be especially emphasized that the prognosis of an "incomplete" form of the disease in a young subject presenting only pigmentation should be carefully guarded. There may be such complications as cosmetic unsightliness, involvement of the central nervous system, with resultant deafness, pain and mental deficiency, development of growth abnormalities and skeletal deformities resulting from osseous involvement, bizarre secondary endocrine manifestations, or, finally, ulceration, hemorrhage, infection or malignant degeneration of tumor growths. In a middle-aged woman repeated pregnancies may stimulate the growth of the cutaneous manifestations to a marked degree and thereby enhance a predisposition to serious complications.⁴⁷ Even for adult patients the prognosis should be guarded, as it has been found that in 72 per cent of the cases of malignant degeneration of benign neurofibroma to sarcoma the disease begins in the third, fourth or fifth, decade.⁴⁸ It is of interest to note that hemorrhage, spontaneous, following slight injury or occurring during the surgical removal of a tumor has been reported as a complication in several instances.⁴⁸ It seems to concern especially the large elephantiasic types of tumor.⁴⁹

No beneficial treatment of Recklinghausen's disease has been found. Women with the "incomplete" form of the disease should be warned about the detrimental effect of pregnancy and the dominant mendelian hereditary tendency passed on to offspring.⁴⁷ As mentioned, organotherapy is practically useless. The tumors are not affected by roentgen or radium therapy. Surgical excision may be resorted to if the tumors become too large, cause pain or interfere with activity. Phillips,⁵⁰ however, warned that these patients are poor surgical risks, as they are particularly susceptible to shock and profuse hemorrhage. If surgical excision of a tumor is to be performed, it should be complete, as partial removal of a neurofibroma predisposes to malignant degeneration.⁴⁴ In some cases malignant transformation occurs after a single operation. In other cases, even after repeated operations, no malignant

47 Sharpe, J. C., and Young, R. H. Neurofibromatosis. The Effect of Pregnancy on the Skin Manifestations, *J. A. M. A.* **106** 682-683 (Feb. 29) 1936.

48 Carrington, G. L., and Bullitt, J. B. Hemorrhage in a Case of von Recklinghausen's Disease, *J. A. M. A.* **87** 166-167 (July 17) 1926. Gordon¹⁶ Knapp⁵

49 Heurer, G. T., and Bell, H. G. Hemorrhage and Infection of Large Tumors (Pachydermatocles) of von Recklinghausen's Disease, *Ann. Surg.* **94** 15-24 (July) 1931.

50 Phillips, H. T., Ferri, L. B., and Morginson, W. I. Surgical Risk Accompanying von Recklinghausen's Disease, *West Virginia M. J.* **28** 263-266 (June) 1932.

changes arise After surgical excision recurrence of the tumor growth may be frequent, it is generally local or regional but may be followed by crops of multiple neurofibromas elsewhere

REPORT OF CASES

CASE 1—H W was a boy aged 15 His father, his grandfather, one aunt and one cousin had cutaneous manifestations of the disease The patient's skin was



Fig 1—Neurofibromatosis, case 1

clear at birth He began to walk at $1\frac{1}{2}$ years of age, but two years later a decided limp developed Brownish pigmentation of the skin appeared when he was 7 The different diseases of childhood had no effect on the pigmentation Progressive enlargement of the left leg, noted during childhood, increased markedly after he was 13 During the past two years there had been an increasing number of areas of pigmentation He had not been aware that any subcutaneous nodules were present until he was examined and a dozen small tumors were felt beneath the skin of the enlarged left leg Roentgenograms of the affected extremity showed a marked growth deformity of the bones, but no subperiosteal neurofibromas could be demonstrated (fig 1)

CASE 2—A W was a man aged 45, father of H W (case 1) His father, sister and son showed cutaneous manifestations of the disease His skin was clear at birth, but during infancy café au lait spots of pigmentation appeared A few nodules appeared on the skin of the back during puberty but had not increased in the last twenty years

CASE 3—M J was a woman aged 42 Her three sisters and three daughters had the disease The entire trunk, arms and thighs were covered with irregular areas of brownish pigmentation with cutaneous and subcutaneous tumors of various sizes Her skin had been clear at birth, but pigmentation appeared shortly afterward and persisted during the various diseases of childhood, puberty and four pregnancies The cutaneous tumors first appeared with the fifth pregnancy and increased with each of two successive pregnancies She had had partial unilateral deafness for six years Her three youngest children had the "incomplete" form of the disease

CASE 4—E J was a girl aged 8, daughter of M J (case 3) Her mother and two younger sisters had cutaneous manifestations The pigmentation of the skin of the neck and body first appeared when she was 3 The usual diseases of childhood had no stimulative effect, and there were no palpable tumors

CASE 5—J J was a girl aged 6, daughter of M J (case 3) Her mother and two sisters had the disease Pigmentation of the body was noted shortly after birth and had increased slightly thereafter No palpable tumors were present

CASE 6—K J was a girl aged 4, daughter of M J (case 3) Her mother and two sisters had the disease One or two rather large café au lait spots of pigmentation appeared on the back during her first year of life

CASE 7—B C was a woman aged 31 (fig 2) There was no family history of the disease When first pregnant, when 19, she noted the appearance of pigmentation and many soft pedunculated tumors over the trunk During two miscarriages and one other pregnancy there has been a definite increase in all the cutaneous manifestations One large painful tumor was removed from the breast, and during the operation there was profuse bleeding The physician made a diagnosis of "nerve tumor" The two living children had no cutaneous manifestations of the disease

CASE 8—D W was a girl aged 10 There was no family history of the disease The skin was clear at birth, but when she was 3 years old a mass appeared in the left cheek and slowly increased to the size of an egg Palpation revealed several discrete painless tumors in the distribution of the left facial nerve After she was 5 years old several other tumors appeared in the skin of the trunk and scalp, accompanied with several small areas of brownish pigmentation on the back A biopsy showed the tumor of the cheek to be a neurofibroma The patient was definitely mentally retarded and was two years behind children of her age at school

CASE 9—M E was a woman aged 38 (fig 3) Her mother, maternal grandfather and two children had evidence of the disease She had had a few spots of pigmentation since childhood There seemed to be no stimulative effect from the usual diseases of childhood, an attack of pneumonia or puberty Since shortly after she learned to walk there had been progressive curvature of the spine Her first two pregnancies had no influence on the skin, but with each of the next four pregnancies cutaneous tumors appeared, with increased pigmentation There had been one miscarriage Her two youngest children, aged 10 and 3 years, had the "incomplete" form of the disease

CASE 10—J E was a girl aged 10, daughter of M E (case 9) Her mother, her grandmother and a sister had the disease Since the age of 2 years the patient had had a few spots of pigmentation on her arms and back, and for the past three years she had been aware of a mass in her right cheek which had steadily become larger

CASE 11—G E was a girl aged 3, daughter of M E (case 9) Her mother, her grandmother and a sister had the disease There were several rather large areas of pigmentation of the skin on the back and upper part of the arms that had



Fig 2—Neurofibromatosis, case 7

appeared first after birth There had been no recent change in the pigmentation or any sign of tumor formation

CASE 12—E C was a woman aged 56 Her father and one daughter had the disease Except for a few so-called freckles over the trunk, the patient's skin was clear before her marriage Accompanying her first and each of seven successive pregnancies, there appeared multiple cutaneous tumors, with an increase in pigmentation Moderate scoliosis developed She had been bedridden for one year because of pain in the left sciatic nerve One adult daughter had the complete form of the disease, and one son was heavily pigmented over the body

CASE 13—N C was a woman aged 24, daughter of G E (case 11) Her mother and grandfather had the disease Since she was a small child the patient had had multiple patches of pigmentation of the trunk When she was 9 years old a small cutaneous tumor developed at the base of the neck, and during puberty several more such tumors appeared Though married, she had not been pregnant



Fig 3—Neurofibromatosis, case 9

CASE 14—J A was a woman aged 34 Her mother, her brother and one son had the disease The skin had been perfectly clear until her first pregnancy, when she noted the sudden appearance of cutaneous pigmentation and tumor growth Following delivery there was a cessation of growth, which did not flare up with her second pregnancy A tumor in the cervical intervertebral foramina resulted in constant pain and scoliosis (fig 4) There was a nontoxic adenoma of the thyroid gland One of her two sons had the "incomplete" form of the disease

CASE 15—F A was a boy aged 7, son of J A (case 14) His mother and grandmother had the disease The patient presented one large area of brown pigmentation on the upper portion of one arm and several areas on the back The pigmentation had come on soon after birth, with no appreciable increase in the past few years (fig 5)

CASE 16—S G was a man aged 21 There was no family history of the disease At birth there were a few areas of light brown pigmentation distributed over the trunk During puberty there was a definite increase in the amount of

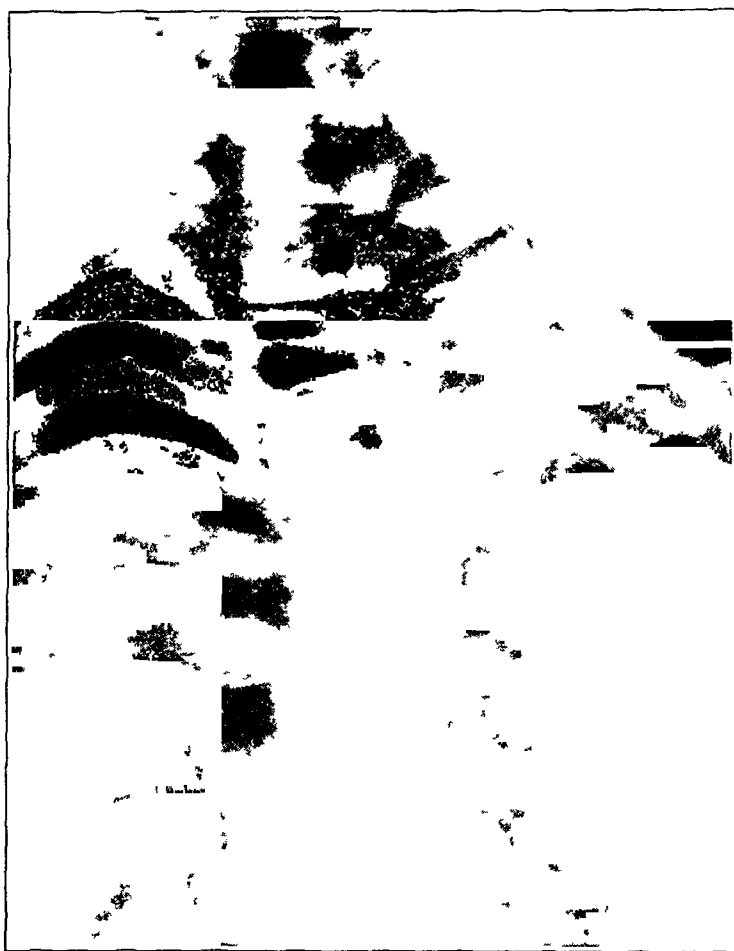


Fig 4—Tumor of the cervical intervertebral foramina, case 14

pigmentation, and multiple cutaneous tumors appeared There had been no recent change in the skin

CASE 17—G H was a woman aged 62 Three brothers, one sister and one daughter had the disease Her skin was clear when she was a child and up to the time of her marriage Though not certain, she believed that the cutaneous pigmentation and the multiple cutaneous and subcutaneous tumors occurred with her first pregnancy and increased with each of four successive pregnancies There was a definite increase in all the cutaneous manifestations during the menopause

CASE 18—F C was a woman aged 23, daughter of G H (case 17) Her mother, one aunt and three uncles had the disease Since infancy she had had a number of pigmented areas over her trunk During childhood multiple cutaneous

tumors appeared over the head, neck and body. The cutaneous changes increased with puberty and again during her first pregnancy, when she was 22. Her baby's skin was clear at birth. The patient presented also unilateral progressive deafness.

CASE 19—E M was a woman aged 66, sister of G H (case 17). One sister, three brothers and one son had the disease. Her skin was clear in childhood and until after her marriage. With the first and each of seven successive pregnancies multiple cutaneous and subcutaneous tumors appeared about the head and neck. The menopause had no effect on the cutaneous signs.

CASE 20—F M was a man aged 25, son of E M (case 19). His mother, an aunt and three uncles had the disease. The skin had been clear until six years previously, when a single large painless tumor suddenly appeared beneath the skin of the left forearm. The trunk showed a large area of pigmentation, which had come on at approximately the same time.



Fig 5—Neurofibromatosis, case 15

CASE 21—S H was a man aged 64, brother of G H and E M (cases 17 and 19). Two sisters and two brothers had the disease. The patient believed he had a few cutaneous tumors at birth, with no increase until the age of puberty, when he became literally covered with the irregular-sized nodules, even over the scalp and palms. A moderate degree of scoliosis was present. Surprisingly enough, there has been little or no change in the size or number of tumors for fifty years (fig 6).

CASE 22—J H was a man aged 61, brother of S H (case 21). Two sisters and two brothers had the disease. Multiple cutaneous tumors had appeared on both arms and a few on the trunk "years ago," with no known change for "a long time."

CASE 23—A H, a woman aged 24, knew of no family history of the disease. Her skin had been clear until puberty, when generalized small cutaneous and subcutaneous tumors and cafe au lait pigmentation appeared. A large plexiform

neurofibroma formed in the left cheek and encroached on the external auditory canal so that hearing was impaired. This tumor was partially removed, a biopsy disclosing that it was a "neurofibroma." In addition, a nontoxic adenoma of the thyroid gland was removed. Though the patient had experienced three pregnancies, the last was the only one to cause any noticeable increase in the size and number



Fig 6—Generalized neurofibromatosis, case 21

of the cutaneous tumors. None of this patient's children had any evidence of the disease.

CASE 24—F S, a woman aged 22, knew of no family history of the disease. There had been no evidence of the disease until after an attack of scarlet fever when she was 19, at which time there was a sudden occurrence of generalized neurofibromatosis, with the formation of a large plexiform neurofibroma on the

left side of the face (fig 7) Partial deafness resulted from this overgrowth of tissue Later the growth was removed

CASE 25—B F was a woman aged 22 One sister and a son had the disease The patient's skin was clear at birth, but pigmentation appeared during infancy After "malarial fever" when she was 9, a few cutaneous tumors appeared on the body Puberty apparently had no appreciable effect on the disease With each of three pregnancies there was a definite increase in all the cutaneous manifestations Her oldest boy, aged 4 years, had the "incomplete" form of the disease

CASE 26—G F was a boy aged 4, son of B F (case 25) His mother and aunt had the disease Several large areas of pigmentation were first noted when he was 1 year old No palpable tumor was present



Fig 7—Neurofibromatosis, case 24

CASE 27—G O, a man aged 36, knew of no family history of the disease Curvature of the spine was first noted when he was 3, and at about the same time two or three irregular areas of brownish pigmentation were apparent on the trunk During puberty a large painless mass appeared below the angle of the right jaw No new tumor had appeared in the last twenty years

CASE 28—B R was a woman aged 28 Her father had the disease Multiple areas of cutaneous pigmentation had been noted since infancy Also during this time beginning scoliosis was noted, which became extreme with advancing years Numerous diseases of childhood had no apparent effect, but the onset of menstruation at the age of 19 caused the appearance of a few cutaneous tumors With each of two pregnancies, both ending in miscarriage, there was a marked increase in the number of tumors until the trunk was almost covered

CASE 29—F R was a man aged 52, father of B R (case 28) He had a doubtful family history of the disease, although his daughter had advanced

neurofibromatosis. His skin was clear when he was a child, but after the age of 14 a large deforming tumor of the gluteal region and several small tumors about the face and neck developed. No new tumors or increase in the size of the present tumors had been noted for the past twenty-five years.

CASE 30—C C, a single woman aged 33, knew of no family history of the disease. The skin was clear at birth, but when she was 2 years old a tumor of the eye appeared. When she was 3 the eye was enucleated. Multiple cutaneous tumors appeared when she was 12, and increased in number during a pregnancy when she was 31. When 33 she had a tumor about the orbit operated on, but the operation was unsuccessful because of excessive hemorrhage. After each of three



Fig 8—Tumor about the orbit, case 30

operations there was growth of the mass (fig 8). The tumor was finally successfully removed by electrocautery. Subsequently sarcomatous (?) metastasis to the lungs developed, and two years later the patient died. No autopsy was made.

CASE 31—F W, a farmer aged 26, knew of no family history of the disease. Tumors of the feet were first noticed when he was 11, and as they became enlarged there was local pain over a period of six years. There were three attempts at operative removal of the painful tumors. Since the first appearance there has been a steady growth of the tumors and an increase in their number. From the time of the first appearance of a tumor about two years passed before it would become painful. The neural status was normal.

COMMENT

Though this paper presents one of the largest series of cases reported, the number is too small to allow any definite conclusive statements relative to the etiology, the occurrence of different clinical types and the possible complications of the disease. However, our figures seem to be in close harmony with those for the larger groups of case reports collected from the literature and should at least serve as a fair guide in a clinical study. Of our thirty-one patients, eleven were males and twenty females. The ages varied from 3 to 66 years. A family history of the disease was obtained in 74 per cent of the cases. The changes in the skin, nerves and bones are summarized in table 1. For the most part, both pigmentation and cutaneous tumors were present at the time of our examination, although seven patients, all less than

TABLE 1—*Types of Clinical Cases*

	Number of Cases
Pigmentation alone	7
Pigmentation and tumors	24
Tumors	
Generalized	17
Plexiform	7
Osseous changes	
Vertebral	6
Long bones	1
Elephantiasis	2
Complications	
Deafness	5
Mental disorder	1
Pain	4
Hemorrhage	3
Malignant growth	1

10 years of age, presented only the "incomplete" pigmentary changes. In all the cases of our series various degrees of pigmentation were noted. The tumors were most commonly generalized, distributed over the trunk and extremities, but seven patients showed the large localized type of plexiform neurofibromas. Evidence of intracranial involvement was suggested in two cases of progressive unilateral deafness, whereas in three other cases deafness was due to encroachment on the external auditory canal by a large plexiform neurofibroma of the face. There were two cases of mental retardation. As a result of tumor growth, pain was the presenting feature in four cases. Osseous changes were noted in seven patients, six having a moderate or severe degree of scoliosis and the remaining patient presenting an osseous deformity of the lower extremity associated with elephantiasis overgrowth of tissue. Elephantiasis nervorum also was present to an extreme degree in one other case. Other associated congenital abnormalities were conspicuously absent.

On inspection of the reports with regard to the type of clinical manifestations which were present during the different age groups, it is of interest and importance that the youngest patients showed only pigmentation of the skin, while the older patients showed cutaneous and subcutaneous tumors and, subsequently, the more serious osseous and elephantiasic changes (table 2). On critical analysis of the histories with respect to the age of the patient at the time of onset and the possible factors influencing exacerbations of the disease, it is significant that in the majority of cases pigmentation began in early infancy and increased during puberty and pregnancy (table 3). In a few cases the

TABLE 2—Types of the Disease at Different Ages

Age, Years	Number of Cases	Pigmentation	Tumors		Osseous Changes	Elephantiasis
			General	Local		
1-10	8	8	1	2		
11-20	1	1	1		1	1
21-30	8	8	7	3	1	
31-40	5	5	4	1	3	1
41-50	2	2	2			
51-60	3	3	2	1		
61-70	4	4	4			

TABLE 3—Clinical Types of the Disease at Different Periods of Life

	Pigmentation		Tumors		Osseous Changes	
	Onset	Exacerbation	Onset	Exacerbation	Onset	Exacerbation
Birth	2		1			
Infancy	16		1		4	
Childhood	1	2	3	1		1
Diseases	1	1	2			
Puberty	4	4	7	4	1	1
Pregnancy	5	8	7	8	2	1
Menopause		1		1		

clinical appearance of tumors was noted during infancy and childhood, but most commonly the tumors became evident during puberty and during pregnancy. In most of our cases the osseous changes began during infancy. In two cases diseases of childhood and the later more serious illnesses apparently had some slight stimulative effect on the course of the disease. Occupation, environment and mental stress had no definite connection with the clinical signs. The surgical removal of small tumors for biopsy and of the larger ones either for the relief of pain or for the cosmetic effect was not followed by any unusual growth phenomena. However, one patient who was operated on subsequently showed malignant degeneration and died of metastatic sarcoma. Severe operative hemorrhage occurred in three cases.

Because of the endocrine theory of the etiology of this disease, a survey of the series for related endocrinopathy was made. Though

menstrual irregularities were fairly frequent and the incidence of miscarriages seemingly was large, no adequate explanation could be found to account for them. The menopause was apparently associated with an increase in the cutaneous changes in one case. Pregnancy occurred fifty times among eleven women, and thirty-six of these pregnancies (72 per cent) caused either the onset or an exacerbation of the disease (table 4). With the exception of three patients, all women in whom a nontoxic adenoma of the thyroid gland was discovered, no other endocrine dysfunction was noted. In addition to a careful history and physical examination in all cases, a more complete study of the endocrine system was possible in six cases. The height, weight, blood pressure, roentgenograms of the bones and sella turcica, basal metabolic rate, dextrose tolerance and calcium and phosphorus content of the blood were studied. In every instance they were found to be within normal

TABLE 4—*Effect of Pregnancy*

	Hereditary	Congenital
Married women	9	2
Number of pregnancies	43	7
Number of miscarriages	9	3
Pregnancies causing onset of exacerbation	32	4
Number of children of such pregnancies	30	4
Number of children with clinical signs	11	0
Number of children without clinical signs	19	4
Pregnancies not causing onset of exacerbation	6	2
Number of children of such pregnancies	4	0
Number of children with clinical signs	0	0
Number of children without clinical signs	4	0

limits. Except for the pigmentation of the skin, we have not been impressed with any clinical similarity between Recklinghausen's disease and Addison's syndrome. We have observed two patients with acromegaly, both of whom had numerous skin tags, sebaceous cysts and soft fibromas about the head and neck and who might have been accidentally included in this series had not biopsy of the skin been made. One case of myxedema in which there were similar cutaneous changes also was excluded.

One of the most outstanding features in the study of our cases was the progressive, changeable course of the disease with the advance of years. The characteristic nosologic concept of this disease has been a static picture of a variety of pathologic changes in the skin, nerves and bones, but our experience has led us to formulate a dynamic presentation of the disorder which stresses the influence of various life experiences and physiologic factors on the natural history of the disease, including such factors as heredity, birth, infancy, childhood, adolescence and pregnancy. The clinical manifestations of the disease during midlife

present a vastly different picture from those during childhood when there may be only a few café au lait spots of pigmentation on the back. As previously pointed out, the wide variations of clinical types in Recklinghausen's disease is well recognized, but that a varying progression of the disease may occur in the subject as a result of the influence of different physiologic factors has not been sufficiently emphasized. The progressive changes in the clinical course may be exemplified by the following hypothetical case. At the age of 3 years a child is brought to a pediatrician because of multiple areas of cutaneous pigmentation, at the age of 7 she is taken to an orthopedist because of beginning scoliosis, at 15 she may notice the appearance of a few soft, painless, cutaneous and subcutaneous tumors and may seek the advice of a dermatologist, and during the early twenties she may ask her obstetrician why the pigmentation and cutaneous tumors become more numerous and prominent during pregnancy. At the age of 30 she may be referred to an otologist, who makes a diagnosis of progressive nerve deafness and sends her to a neurosurgeon for removal of the bilateral tumors of the acoustic nerve. A few years later, because of constant pain in the left thigh, she may consult a neurologist, who will find involvement of the sciatic nerve. Later, an internist may advise surgical removal of a large pendulous tumor of the breast, which has undergone malignant degeneration. Thus, the patient reaches the pathologist's postmortem table. At any time during the entire life of such a patient some specialist might give a diagnosis of neurofibromatosis without truly appreciating the complete evolution of the disease.

The question naturally arises. What common factor or factors are present during the different age periods that cause such steplike exacerbations and so influence the course of the disease? From a study of our patients we suggest that from an etiologic standpoint a division of the patients into two groups is possible. (1) patients without any family history of the disease, who, at least in our experience, do not pass the disease on to their offspring—patients with the so-called congenital type—and (2) the larger group of patients who show a family history of the disease and who tend to pass the inheritance on to their children—patients with the so-called inherited type. The affected offspring of patients with the inherited type of disease may or may not present evidence of the disease at birth, but a latent tissue abnormality is present nevertheless. On the other hand, in patients without a family history of the disease, it is conceivable that for some unknown reason there is a congenital maldevelopment of some mesodermal tissue in utero which may be clinically manifest at birth or may lie as a dormant embryonic arrest for a number of years. Whether the condition is inherited or congenital in origin, its potential

possibilities are the same. Its embryonic character is subject to the stimulation of growth activity through infancy, childhood and puberty, just as all other normal tissue is influenced during these periods. If the clinical signs are present at birth, they may continue to increase during the first two decades of life, or, if absent, they may become apparent for the first time during this period. In our group of men and non-pregnant women between 20 and 25 years of age, few new tumors were noted, and in some instances there seemed to be a cessation of the growth of the nodules. In the occasional case after this age, the older and larger tumors continue to grow slowly. It seems possible, therefore, that two factors may be necessary for the production of this disease: (1) primary maldevelopment of mesodermal tissue, which may be either inherited or congenital in origin, and (2) a secondary quantitative response of this abnormal tissue to the normal physiologic growth stimulus that is supplied during the first two decades of life.

If this hypothesis is correct, how can one explain the exacerbations of the disease during pregnancy? It might be reasonable to suppose that in any case of Recklinghausen's disease of either the inherited or the congenital type the latent embryonic arrests in the mother are powerfully stimulated by the growing fetal tissue and that a clinical flare-up of the disease is noted. This exacerbation of the cutaneous manifestations may not occur during the first or even the second pregnancy but may be noted during the third or fourth pregnancy. It appears, however, that once an exacerbation occurs during pregnancy, with each succeeding pregnancy there will be a similar response. Emge⁵¹ stated as his conclusion that "neoplastic tissue sensitive to hormonal stimuli may exhibit increased activity during pregnancy," and though a dermoid cyst ordinarily does not enlarge with pregnancy, a cystic teratoma may, at times, enlarge rapidly. He pointed out further the well known fact that a benign adenoma of the breast responds to the stimulus of pregnancy in the same ratio as does normal mammary tissue and that the activating factor must necessarily be hormonal in origin. It is not surprising, therefore, that carcinoma of the breast is unfavorably influenced by pregnancy. One interesting and perhaps significant fact revealed by our series is that pregnancy caused an exacerbation in the cutaneous manifestations in approximately 72 per cent of the cases of inherited Recklinghausen's disease and that in over one third of the children of these particular pregnancies the disease has developed. As the children grow older we expect more of them to show clinical manifestations of involvement. On the other hand, when the pregnancy did not cause the onset or an exacerbation we have not yet noted develop-

⁵¹ Emge, L. A. Influence of Pregnancy on Tumor Growth, *Am J Obst & Gynec* 28: 682-697 (Nov.) 1934.

ment of the disease in the offspring. It is also pertinent to point out that none of the children of parents who carry the congenital type of disease show any clinical evidence of pigmentation or tumor growth.

That pregnancy may influence the course of Recklinghausen's disease is of considerable importance in considering the prognosis and treatment. Each additional pregnancy adds to the possibility of exacerbation and spread of the various tumor growths, which, in turn, may lead to more serious complications, such as involvement of the central nervous system, osseous changes, disfigurement or malignant degeneration. The chances of such complications are higher with the advance of years and repeated pregnancies, so that the prognosis for young persons should be guarded. After experiencing alarming changes in the skin several of our patients have requested sterilization. Observing the same tell-tale brownish pigmentation of the skin in their children that they themselves once had, they have insisted that no further pregnancies be permitted. If any part of neurofibromatosis can be prevented, it seems that pregnancy offers the main hope of control. In cases of inherited neurofibromatosis the disease is usually made worse by pregnancy, and there is a 50 per cent chance that the disease will develop in the offspring. In the case of males with a family history of the disease the same holds true for their offspring. Though pregnancy will cause an exacerbation of the disease in a woman with the congenital type of neurofibromatosis, the disease does not and theoretically should not develop in the children.

SUMMARY

A review of the literature on Recklinghausen's disease reveals a variety of etiologic factors, a tendency to classify the features of the disease into clinical types, the controversy as to whether the tumors are mesodermal or ectodermal in origin and the utter lack of any successful treatment.

A study of our thirty-one cases of Recklinghausen's disease fails to reveal any new clinical features or remarkable combinations of previously described manifestations. However, from this study certain conclusions have emerged. It is suggested that from a congenital or inherited mesodermal abnormality an embryonic tissue arrest is formed, which at birth or during infancy, childhood, puberty or pregnancy may become clinically manifest, depending on its response to the stimulation of the normal physiologic growth factor. This reaction to the influence of physiologic factors and life experiences leads to the progressive and changeable course of the disease. The clinical features that any particular patient may present will be dependent on his age, the congenital factors and his individual sensitivity to stimulating influences.

Of all the influences studied in the thirty-one cases, pregnancy produced the most stimulative effect in the progressive course of the disease. This effect has been mentioned in the past, but its dramatic nature has not been fully appreciated. In this disease, which is in a large percentage of cases hereditary and which is without beneficial treatment, it seems that avoidance of pregnancy affords the chief opportunity for control and arrest.

It is hoped that further attention to the history of the disease during the life of affected subjects, rather than a consideration of the more classic, static, nosologic cross-section of the disease that the patients present at any life period, will be productive of a more helpful management.

CONCLUSIONS

A review of thirty-one cases of Recklinghausen's disease has been presented with reference to the clinical manifestations at different life periods.

Recklinghausen's disease is caused by a reaction of mesodermal tissue that presents a variable picture, with changes over a period of years resulting from the influence of various life experiences and physiologic growth factors.

Pregnancy is the most potent factor in stimulating the progressive course of the disease. The avoidance of pregnancy seems to offer the greatest opportunity for the arrest of the progressive course and control of the disease.

Drs. H. F. Tyler, C. C. Tomlinson, O. J. Cameron, J. M. Christlieb and J. R. Redgwick permitted us to examine their patients.

ABSTRACT OF DISCUSSION

DR. W. M. KETCHAM, Kansas City, Mo. Neurofibromas are simple tumors which occur in connection with superficial or deep nerves. They grow from the perineurium and endoneurium and as they increase in size the nerve fibers become expanded over or buried in them. The tumors may be rounded and either hard or soft and are frequently multiple. Function is not necessarily affected by them.

Neurofibromas are divided into two groups—central and peripheral. Central neurofibromas occur commonly within the skull, particularly in relation to the root of the eighth nerve, and are known as neurofibromas of the acoustic nerve. The fibromas of the skin and deep tissues of the limbs are of this type. The tumors arise from the motor and sensory nerves rather than from the sympathetic fibers.

The authors suggest the etiologic classification—congenital and hereditary tumors.

Cutaneous neurofibromas may be single or multiple. The condition known as neurofibromatosis, molluscum fibrosum or Recklinghausen's disease is characterized by multiple neurofibromas, with localized distribution to single nerve trunks or to the whole body.

Larger tumors frequently have pedicles and become pendulous. Thickening and pigmentation of the overlying skin develop, and occasionally there is softening or maldevelopment of the bones. Cerebral tumors are rare. Slowly progressive but essentially benign, the tumors may be removed without recurrence.

The authors show that the physiologic epochs of infancy, childhood and especially adolescence and pregnancy exert a great influence in changing the characteristics of this disease. Pregnancy is the greatest factor. Neurofibromatosis, however, is present in men also, so that if there is an endocrine growth-stimulating factor, it must be one factor or a combination of factors peculiar to both sexes. As a rule, pregnancy increases the basal metabolic rate from 10 to 20 per cent plus, so that normal readings indicate a relative deficiency. During pregnancy the cellular activity is increased and may definitely influence the frequent activation and growth of neurofibromas. Theoretically there should be an increase in the secretion of the eosinophilic cells of the anterior pituitary gland during pregnancy, so as to account for the remarkable stimulation to the tissue of the growing fetus. I suggest trying combinations of thyroid, solution of adrenal cortex and a preparation of the anterior lobe of the pituitary gland containing the growth-stimulating hormone if there are any evident changes after a year's observation. The most important hormone should be the growth-stimulating principle inherent in the anterior lobe of the pituitary gland, because the periods of the greatest growth of neurofibromas are during adolescence and pregnancy.

DR J J ELLER, New York. Most dermatologists feel that this disease is hereditary, even though at times it is difficult to bring out in the history that a parent or grandparent showed signs of the disease. I have reported on a few cases in which certain members of a family had distinct and well developed neurofibromatosis and other members in the third or fourth decade of life showed only slight but typical pigmentation of Recklinghausen's disease, in other words, abortive forms.

This particular type of the disease is of interest to physicians for the following reasons. Some of these patients appear with vague muscular or osseous pains or some aural disturbance of vague etiology or even an ocular disturbance. Perhaps, with further study, it would be found that there was a family history of Recklinghausen's disease of the abortive type.

No local destruction that I know of—and my colleagues and I have experimented with various types of removal by surgical measures and coagulation—in any way affects the tumors. They always recur. No glandular therapy that is known today has in any way affected the course of this condition. I agree with Drs Sharpe and Young that sterilization is the one hope, in order to prevent not only exacerbations of the disease in women but also the bringing forth of children who would suffer from this serious malady.

Regarding the mental changes about which so much is said in the literature, I consider that mental aberration is a rarity rather than the rule.

DR RICHARD H YOUNG, Omaha. Dr Ketcham brought out the fact that there was also the cranial type of neurofibromatosis. In discussing that point it is well to mention that the ordinary tumor of the eighth nerve is a solitary tumor and of a different type histologically. It has been called by Penfield a perineurial fibroblastoma. Of course, neurofibroma of the eighth nerve does occur in this disease.

In reference to the effect of pregnancy, it was of interest to us that in our male patients we saw practically no exacerbation or increase in the size or in the number of the tumors after the period of adolescence.

I wish to emphasize the fact that we have been chiefly interested in the natural history of this disease and the dynamic factor that influences the course. We have been interested also in the clinical types or cross-section view of the disorder as it appears at the different periods of life. The chief exciting factors seem to be the physiologic changes of infancy, puberty and pregnancy, and of these, pregnancy has been the least appreciated and yet, in our series, provoked the most dramatic changes.

In this disease, for which there is no specific treatment, it seems to us the avoidance of the possible stimulating factors offers the chief opportunity for control.

Progress in Internal Medicine

DISEASES OF METABOLISM AND NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

RUSSELL M WILDER, PH D, M D

AND

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ROCHESTER, MINN

I DISEASES OF METABOLISM

By DR WILDER

DIABETES MELLITUS .

Protamine Insulin—The discovery of Hagedorn¹ that protamines will combine loosely with insulin, giving flocculant precipitates that are relatively insoluble in the fluids of the tissues, whereby prolonged hypoglycemic effects are obtained, has received much attention during this past year. All the American and Canadian manufacturers of insulin, cooperating with the Insulin Committee of Toronto, have undertaken the manufacture of such preparations. A large number of clinicians have been supplied with material for trial, and several thousand patients have already received treatment with the new compounds.

The reports of clinicians that have appeared are those of Hagedorn,¹ Krarup,² Root,³ Lawrence,⁴ Leyton,⁵ Kerr,⁶ Sprague,⁷ Rabinowitch,⁸

From the Division of Medicine, the Mayo Clinic

The section on "Nutrition" will be published in the March issue of this journal

1 Hagedorn, H C, Jensen, B Norman, Krarup, N B, and Wodstrup, I. Protamine Insulinate, J A M A **106** 177-180 (Jan 18) 1936

2 Krarup, N B. Clinical Investigations into the Action of Protamine-Insulin, Copenhagen, G E C Gad, 1935

3 Root, H F, White, Priscilla, Marble, Alexander, and Stotz, E H. Clinical Experience with Protamine Insulinate, J A M A **106** 180-183 (Jan 18) 1936

4 Lawrence, R D, and Archer, Nora. Some Experiments with Protamine Insulinate, Brit M J **1** 747-749 (April 11) 1936

5 Leyton, O. Protamine Insulinate, Brit M J **1** 443 (Feb 29) 1936

6 Kerr, R B, Best, C H, Campbell, W R, and Fletcher, A A. Protamine Insulin, Canad M A J **34** 400-401 (April) 1936

(Footnotes continued on next page)

Winnett,⁹ Joslin,¹⁰ Black,¹¹ Bowcock,¹² Smith¹³ and Allen¹⁴ and the associates of these workers. The verdict on the whole is highly favorable and almost unanimous. Fewer injections and, in most cases, a smaller number of units are required to maintain a satisfactory level of sugar in the blood. The reactions are fewer and less severe, and the general health of the patient frequently is improved. These are important advantages. However, apprehension is expressed by many that widespread use of the new preparation, involving as it does a technic which differs in important particulars from that required for giving regular insulin, will result in many serious accidents. It is highly important, therefore, that physicians acquaint themselves with what now has been published about protamine insulin before prescribing it.

As originally distributed, protamine insulin was supplied in two vials, one containing 4 cc of U 50 water-soluble insulin, the other 1 cc of a suitably buffered solution of protamine. The directions stated that the contents of the two vials were to be combined shortly before using. The resulting precipitate was stable only for a limited number of days. Later, it was found that the addition of traces of zinc, 0.2 mg per hundred units of insulin, imparts stability to the precipitate and, therefore, recently the material for distribution has been supplied already mixed in one vial. Hereafter in this paper, unless otherwise stated, protamine insulin with zinc added in this proportion will be meant whenever the term protamine insulin is employed. It is expected that

7 Sprague, R. G., Blum, B. B., Osterberg, A. E., Kepler, E. J., and Wilder, R. M. Clinical Observations with Insulin Protamine Compounds, *J. A. M. A.* **106** 1701-1705 (May 16) 1936. Wilder, R. M. The New Insulin, *Minnesota Med.* **20** 6-15 (Jan.) 1937.

8 (a) Rabinowitch, I. M., Fowler, A. F., and Corcoran, A. C. Observations on the Action of Protamine and Insulin in the Treatment of Diabetes Mellitus, *Canad. M. A. J.* **35** 124-129 (Aug.) 1936. (b) Rabinowitch, I. M., Foster, J. S., Fowler, A. F., and Corcoran, A. C. Clinical Experiences with Protamine-Zinc-Insulin and Other Mixtures of Zinc and Insulin in Diabetes Mellitus, *ibid.* **35** 239-252 (Sept.) 1936.

9 Winnett, E. B. The Treatment of Diabetes with Protamine Insulin, *J. Iowa M. Soc.* **26** 231-237 (May) 1936.

10 Joslin, E. P., Root, H. F., Marble, Alexander, White, Priscilla, Joslin, A. P., and Lynch, G. W. (a) Protamine Insulin, *New England J. Med.* **214** 1079-1085 (May 28), (b) Protamine Insulin, *Tr. A. Am. Physicians* **51** 174-187 1936.

11 Black, D. R. Protamine Insulin, *J. Missouri M. A.* **33** 212-215 (June) 1936.

12 Bowcock, Harold. Observations on the Treatment of Diabetes with Protamine Insulin in Office and Hospital, *South M. J.* **29** 701-704 (July) 1936.

13 Smith, B. Clinical Studies with Protamine-Insulin, *California & West. Med.* **45** 144-148 (Aug.) 1936.

14 Allen, F. M. Some Difficulties Arising in the Use of Protamine Insulinate, *J. A. M. A.* **107** 430-431 (Aug. 8) 1936.

the product will be placed on the market shortly after Jan 1, 1937, and that the cost to the patient will not exceed that of treatment with regular insulin

Some objection was raised to the addition of zinc, and for a time calcium was used. It improved the stability of the precipitate but not so satisfactorily as zinc, it failed also to prolong the time of action and for these reasons was abandoned. As a matter of fact, fear of the long-continued use of zinc in such minute doses is unjustified. Zinc commonly is present in the pancreas in considerable amount, and insulin always has contained traces of zinc (from 0.05 or less to 0.1 mg or more per thousand units). Rabinowitch¹⁵ and his associates have attended to this question. They have pointed out that zinc does not accumulate in the blood of workers who for years have been exposed to its fumes and, furthermore, that zinc has been added to the rations of animals (rats) observed through three generations without producing deleterious effects of any kind.

Duration of Action The length of time during which an effect can be maintained by a single injection of protamine insulin seems to be much greater in man than in animals. It is commonly supposed that this is accounted for by the larger size of the dose given. The duration of the action is influenced by the size of the dose and by the amount of sugar to be metabolized. The injection of a number of units inadequate for maintenance may reveal little evidence of any prolongation of action (Lawrence and Archer⁴), and even a maintenance dose will act for a shorter time when given with food than when food is withheld. The following studies are cited in illustration.

A patient with severe diabetes was fed at two hour intervals with a mixture of milk, cream and syrup, each feeding representing one twelfth of what previously had been the daily allowance of carbohydrate, protein and fat. Under these circumstances the activity of a large dose (132 units) of protamine insulin containing calcium (1 mg per hundred units) was exhausted by the end of twenty-four hours. The sugar content by that time had reached the original value, and sugar was appearing in the urine. At the end of twenty-eight hours acetone was present in the urine, and the balance for nitrogen had become negative. At the end of thirty-six hours the carbohydrate-combining power of the plasma had fallen to 32.4 volumes per cent, and the patient exhibited the signs and symptoms of diabetic acidosis (fig 1). There thus was no reason to believe that the insulin injected was acting after thirty-six hours.

A second patient with diabetes as severe as this was given 70 units of plain protamine insulin and thereafter no food for fifty-seven hours¹⁵. The sugar value

15 The subject of the first study had not received protamine insulin previously and had been taking daily 88 units of regular insulin in four divided doses. For reasons which will be given later it was assumed that not more than two thirds of the protamine insulin administered would come into play within the first twenty-four hours, therefore, the dose was made to equal 1.5 times 88, or 132 units. The subject of the second study had been maintained in equilibrium beforehand with 70 units of plain protamine insulin a day.

fell gradually to the hypoglycemic level and remained there until the fifty-seventh hour, when feeding was resumed. The patient exhibited no symptoms of hypoglycemia until the end of the period, and clearly the insulin was continuing to act fifty-seven hours after injection (fig 2)

Added zinc prolongs the activity of insulin and protamine insulin. The duration of activity of the protamine insulin used in the first of the two studies just cited, when compared with another observation

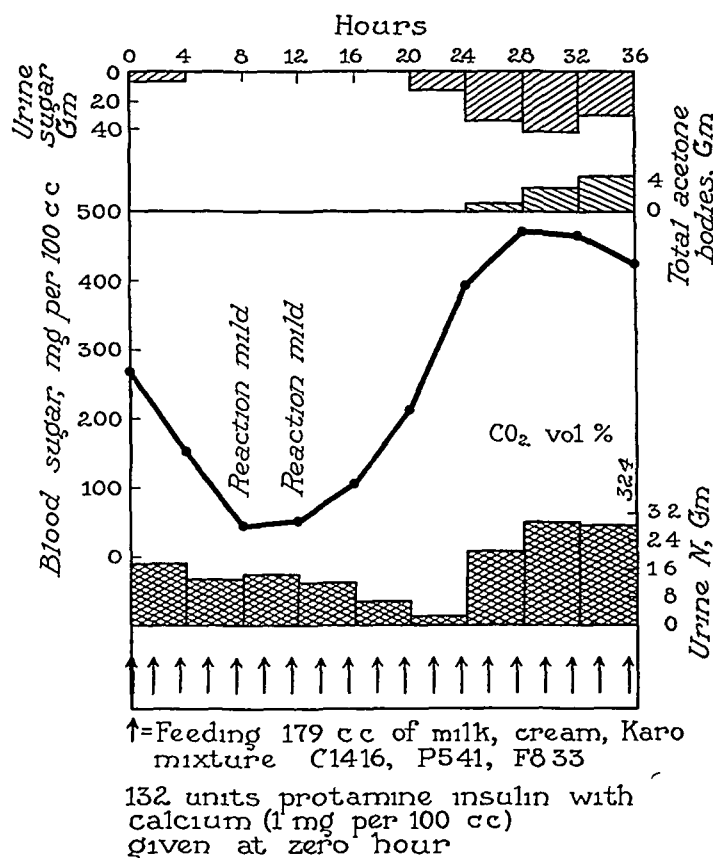


Fig 1—The duration of action of protamine insulin containing calcium in a woman aged 32 who was receiving food at two hour intervals

made of the same patient, illustrates effectively the further prolongation of action imparted to protamine insulin by the addition of zinc

After the first patient had been given only regular insulin for three days, another study was carried out using protamine insulin containing 2 mg of calcium per hundred units. The result was the same, if anything the duration of activity was even a little shorter. Then for three days, only regular insulin was used, and the effect of administering 132 units of protamine insulin containing 0.2 mg of zinc per hundred units was observed. This time, after thirty-six hours the patient remained free from acidosis and was only beginning to excrete sugar (fig 3)

Why the addition of zinc thus should prolong the action of protamine insulin has not been explained other than by the assumption that

it behaves as a catalyst. Not only zinc but cobalt and nickel occur in the pancreas in appreciable quantities, as has been demonstrated by Fisher and Scott,¹⁶ and various authors have attributed significance to the presence of these ions of heavy metals. Thus, Bertrand and Mâcheboeuf¹⁷ noted that small amounts of cobalt and nickel administered with insulin would increase the quantity of sugar utilized, Maxwell and Bischoff¹⁸ reported that the addition of basic ferric chloride had a similar effect, and Kylin¹⁹ found that potassium ions increased the sugar content of the blood and depressed the action of insulin, whereas calcium ions had the opposite effect. Fazekas and Himwich²⁰ have

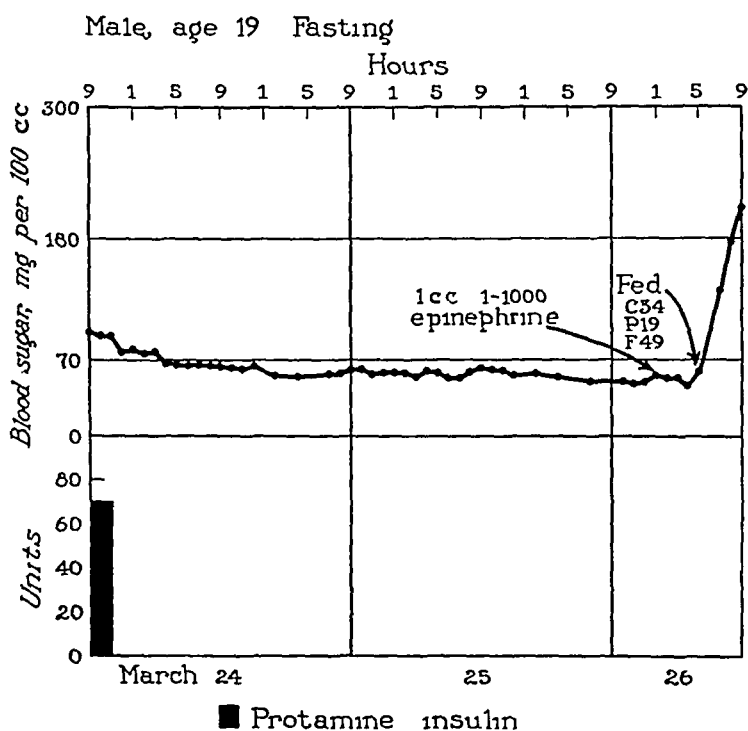


Fig 2—The duration of action of protamine insulin during fasting in a man aged 19

reported that salts of aluminum retard the action of insulin. The amount of zinc in the pancreas is greater than that of these other metals, and zinc has a greater effect on the activity of insulin than either cobalt or potassium. Its action when added to regular insulin, according to

16 Fisher, A. M., and Scott, D. A. Zinc Content of Bovine Pancreas, *Biochem J* **29** 1055-1058, 1935

17 Bertrand and Mâcheboeuf, quoted by Scott and Fisher²¹

18 Maxwell and Bischoff, quoted by Scott and Fisher²¹

19 Kyling, quoted by Scott and Fisher²¹

20 Fazekas, J. F., and Himwich, H. E. The Effect of Zinc and Aluminum on the Hypoglycemic Action of Insulin, *J Pharmacol & Exper Therap* **58** 260-263 (Nov) 1936

Scott and Fisher,²¹ is to extend considerably the period of hypoglycemia (fig 4) Kerr and his associates²² called attention to a difficulty that every one treating diabetes seems to have encountered of late, namely that many more diabetic patients than formerly require more frequent injections of regular insulin. They explained this on the basis of the greater purity of the insulin available in recent years and by the fact that the manufacturers, in securing this greater purity, have diminished

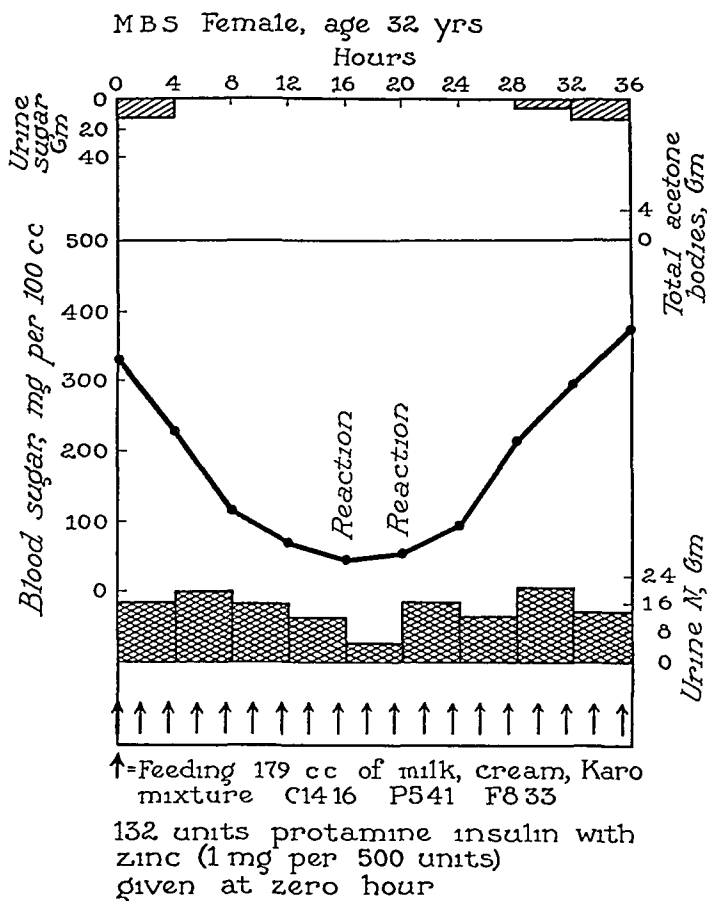


Fig 3—The duration of action of protamine insulin containing zinc in a woman aged 32 who was receiving food at two hour intervals

the previously higher content of metallic salts, principally that of zinc. This, I think, must be the case, because recently, by using regular insulin to which zinc has been added, I have found it possible to maintain several patients with two injections a day who previously required four injections of commercial insulin.

21 Scott, D A, and Fisher, A M The Effect of Zinc Salts on the Action of Insulin, *J Pharmacol & Exper Therap* **55** 206-221 (Oct) 1935

22 Kerr, R B, Best, C H, Campbell, W R, and Fletcher, A A Protamine Insulin, *Canad Pub Health J* **27** 157-159 (April) 1936

Crystalline Insulin Sahyun²³ crystallized insulin and found that a solution of it had an action that was considerably prolonged as compared with that of commercial insulin. His preparation contained zinc. The presence of traces of zinc or other heavy metals is necessary, indeed, to effect crystallization of insulin, as had been shown before by Scott²⁴. But whether or not the longer activity of Sahyun's crystalline insulin is attributable to the zinc is unsettled, Sahyun has said not. The material he prepared for distribution to a few clinicians for trial contained only 0.9 mg of zinc per thousand units, and by recrystallization he was able to reduce this content to as little as 0.2 or 0.3 mg per thousand units without loss of prolonged activity. Such minute amounts of zinc will not prolong the action of regular insulin when added to it, indeed, they are smaller than the amounts formerly contained in com-

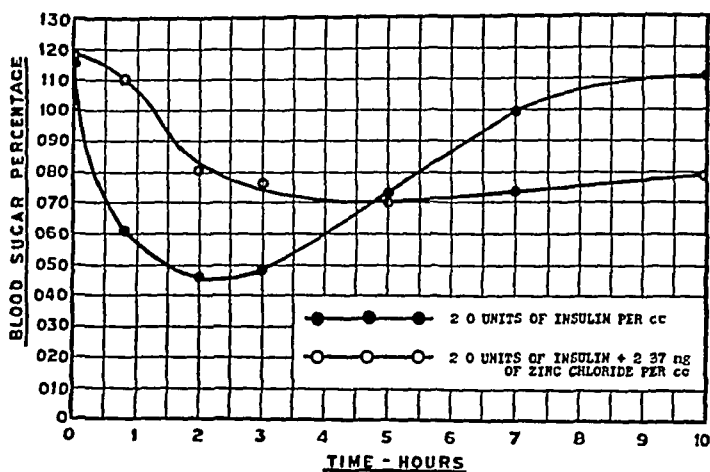


Fig. 4—The effect of added zinc on the duration of action of regular insulin (from Scott and Fisher)

mercial insulin. Sahyun therefore stated that he supposed that his preparation must owe its prolonged action either to some peculiar chemical reaction between the zinc and the insulin or to some racemization within the large molecule of insulin. On the other hand, spectroscopic analysis of samples of Sahyun's preparation made by Foster revealed a zinc content of from 0.437 to 1.15 mg per five hundred units, and little difference was found between the action of these samples and crystalline insulin which was prepared by the usual method in the Connaught Laboratories. The duration of action of Sahyun's preparation is such that satisfactory control of hyperglycemia can be obtained in most cases with no more than two injections a day, it is not enough to effect control with only one injection a day, as is illustrated in figure 5.

²³ Sahyun, M. Personal communication to the authors.

²⁴ Scott, D. A. Crystalline Insulin, *Biochem J* **28** 1592-1602, 1934.

Experience at the Mayo Clinic with this preparation is not greatly different from that reported by Altshuler and Leiser,²⁵ who found that the duration of action of crystalline insulin does not exceed thirteen or fourteen hours but that the use of this preparation permits better control with fewer doses and fewer total units than is possible with ordinary insulin. Freund and Adler²⁶ apparently did not take the fullest advantage of the long action of protamine insulin and gave no less than two injections a day. For this reason crystalline insulin in their experience did not appear at a disadvantage.

Another report by Mains and McMullen²⁷ is more difficult to interpret. Apparently they were dealing with cases of milder diabetes.

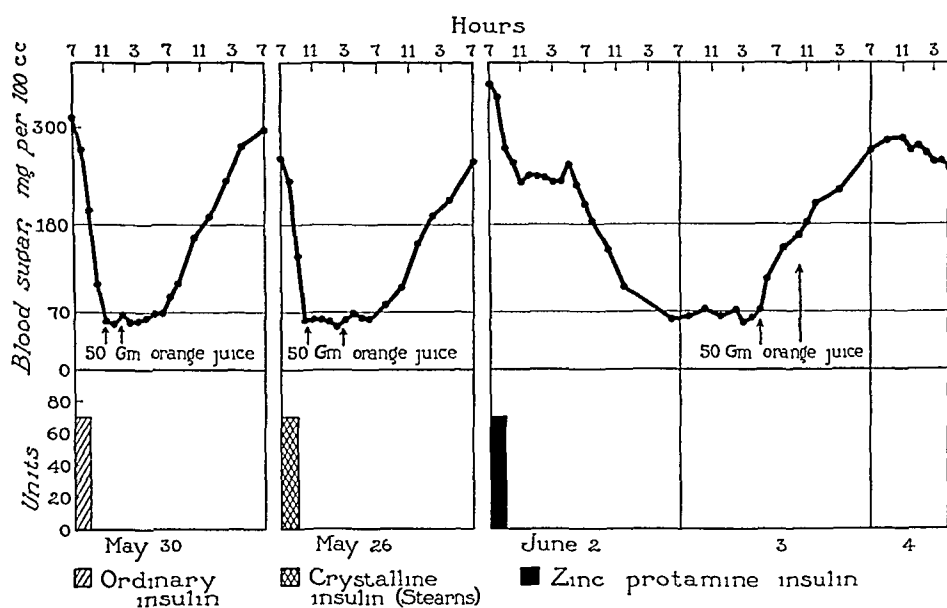


Fig 5—A comparative study of the action on the sugar content of the blood of a fasting diabetic man aged 19 of regular insulin, Stearn's crystalline insulin (Sahvun) and zinc protamine insulin. For more than three days before each observation the patient was given 70 units of regular insulin daily in divided doses and a diet containing 150 Gm of carbohydrate. The evidence from this and similar studies indicates that crystalline insulin acts for little more than twelve hours.

Many of their patients suffered from arteriosclerotic complications, this being a type of diabetes in which not infrequently large overdoses

25 Altshuler, S. S., and Leiser, Rudolph. Clinical Experience with an Improved Crystalline Insulin, *J A M A* **107** 1626-1629 (Nov 14) 1936.

26 Freund, H. A., and Adler, Sidney. Effects of Standard, Protamine and Crystalline Insulin on Blood Sugar Levels, *J A M A* **107** 573-577 (Aug 22) 1936.

27 Mains, M. P., and McMullen, C. J. The Clinical Investigation of an Improved Crystalline Insulin. Preliminary Report, *J A M A* **107** 959-962 (Sept 19) 1936.

of insulin can be tolerated without symptoms of reactions. Under these circumstances it appeared to these authors that the sugar level of the blood could be satisfactorily maintained with one injection a day of crystalline insulin. Rabinowitch and his colleagues also found in some cases that the prolongation of action of crystalline insulin equaled that of plain protamine insulin, although it was never as great as that of protamine zinc insulin. Their data suggest that the prolongation of action of crystalline insulin is due to its content of zinc. They obtained equally good, and in some cases better, results by the simple addition of zinc to regular insulin and found that large amounts of zinc, enough, for example, to provide a 0.4 per cent concentration, led to actual inhibition of the action of the insulin in 1 case and to great retardation of action in others.

Other insulins with a prolonged action have been originated. One is insulin tannate, which is prepared by Bischoff. It was studied clinically by Gray.²⁸ A suitable solution of tannic acid is added to regular insulin of U 100 strength, so that the resulting mixture contains 3 mg. of tannic acid per hundred units. The addition must be made immediately before injection. Erythema and subcutaneous swellings occasionally were encountered. These are disadvantages. Another preparation is that of Klein and Grosse.²⁹ Their "Insulin-Durant" consists of a viscous mixture of lipoids which requires special syringes and needles for injection. Leyton³⁰ in London in 1929 and Bernhardt and Strauch³¹ in Berlin in 1926 also attempted to retard the action of insulin, resorting to mixing it with oil. Bernhardt and Strauch really were the pioneers in this endeavor to prolong the action of insulin.

Methods of Administering Protamine Insulin. Hagedorn, Jensen, Kraup and Wodstrup,¹ who were the first to report on the clinical use of protamine, gave in most cases an injection of protamine insulin in the evening and one of regular insulin in the morning. Root, White, Maible and Stotz³ at first either followed that schedule or gave two injections a day of protamine insulin. Sprague and his associates,³²

28 Gray, P. A. The Treatment of Diabetes Mellitus with Insoluble Insulin Compounds, *Endocrinology* **20** 461-472 (July) 1936.

29 Klein, G., and Grosse, A. Theoretische und praktische Ergebnisse mit parenteralen Depots, *Ztschr. f. d. ges. exper. Med.* **98** 623-650, 1936. Katsch, G., Scholderer, H., and Klatt, K. Depotinsulin, *Ztschr. f. klin. Med.* **129** 608-626, 1936.

30 Leyton, O. The Administration of Insulin in Suspension, *Lancet* **1** 756-759 (April 13) 1929, *Clin. Med. & Surg.* **36** 299-302 (May) 1929.

31 Bernhardt, Hermann, and Strauch, C. B. Ueber parenteral Depots wasserloslicher Medikamente, *Ztschr. f. klin. Med.* **104** 744-766, 1926.

32 Sprague, Blum, Osterberg, Kepler and Wilder.⁷ Wilder, R. M. Clinical Investigations with Insulin Protamine Compound, *Proc. Staff Meet., Mayo Clin.* **11** 257-258 (April 22) 1936.

impressed by the evidence that the full effect of an injection of protamine insulin was not exhausted until some time after the first twenty-four hours, were led to treat patients with one injection, giving the entire dose for the day in the morning before breakfast. This procedure was adopted also by Campbell³³ and later by Joslin^{10b} and Rabinowitch^{8b} and their associates and by others. It usually is satisfactory, although in cases of severe diabetes a supplementary dose of regular insulin is required to prevent glycosuria after meals. There is no reason to fear the relatively large size of the single dose if the injection is made in the morning, because before the peak effect is obtained the patient has received both breakfast and the noon meal, and these prevent excessive lowering of the sugar content of the blood. The principal difficulty at present with the single morning injection is that the Insulin Committee in Toronto has consented thus far to the distribution of protamine insulin only in the U 40 strength. Their explanation is that the duration of action is affected by the volume of the injected material, but in consequence of being limited to material of this strength patients requiring more than 40 units for the day must either use a larger volume of material than is pleasant or divide the dose and make two simultaneous injections. It is to be hoped that protamine insulin of U 80 strength will be found to be equally effective.

An advantage of giving all the insulin for the day in a single injection and making this injection before breakfast is that by this technique the qualitative test of the morning urine for sugar becomes an accurate guide to dosage. Tests at other times of the day reflect the hyperglycemic effect of meals, and such postprandial hyperglycemia and glycosuria may occur even when the dose of protamine insulin is so large that it will provoke a reaction at night. When the entire dose is given before breakfast, the morning test, if positive, shows that the dose is inadequate and can be increased with safety. If negative, it indicates that the dose is as much as can be tolerated, and any evidence of a reaction then becomes an indication for a smaller dose.

Diets with Protamine Insulin. Campbell,³³ Joslin^{10b} and Sprague⁷ and their colleagues have expressed the opinion that greater latitude in the amounts of foods may be allowed to patients using protamine insulin. Good results have been obtained with diets high in carbohydrate by Rabinowitch and with diets high in fat and low in carbohydrate by Campbell. On the whole, according to Campbell's experience, patients receiving diets moderately low in carbohydrate have lent themselves more readily to treatment with a single large dose than patients on other types of diet.

33 Campbell, W. R., Fletcher, A. A., and Keri, R. B. Protamine Insulin in the Treatment of Diabetes Mellitus, *Tr. A. Am. Physicians* **51** 161-173, 1936.

Economy Effected with Protamine Insulin With protamine insulin, especially that to which zinc has been added, the average patient requires a smaller number of units a day. The average saving has been about 25 per cent, but in occasional cases the saving may be much greater. Rabinowitch and his colleagues attributed this need for less insulin to an increased sensitivity to insulin imparted by the zinc, but as yet the evidence for this is not entirely satisfactory. The facts suggest that insulin is protected by zinc or bound to the cell for a longer period, instead of being rushed past the liver and other tissues, perhaps to be excreted. It is as if the zinc acted like a hook or, to use Ehrlich's metaphor, like a side chain. The saving effected is not at once apparent when protamine insulin is substituted for regular insulin, indeed, for the first few days a larger number of units may be necessary, or a daily dose of protamine insulin as large as the number of units of regular insulin used before must be supplemented with additional regular insulin. This is because the action of the protamine preparation is retarded so that the full effect of the dose given on the first and second days is not obtained. My colleagues and I have found that the substitution can be made satisfactorily if four tenths of the previous dose of regular insulin is administered on the first day as a supplement and two tenths of the previous dose on the second day. Later, the number of units of protamine insulin usually can be reduced. Campbell³³ recommended giving from 75 to 100 per cent of the previous dose of regular insulin as protamine insulin in a single morning dose, accompanied the first day with about 60 per cent of the previous dose of regular insulin and on the second with 30 per cent of the previous dose.

Effectiveness of Protamine Insulin in Severe Acidosis It seemed at first that the retarded action of protamine insulin made it undesirable for the treatment of coma, infection and other emergencies in which quick action is important. This is not strictly true, as was shown by Rabinowitch and his colleagues and as is indicated by experience at the Mayo Clinic. Recently 75 units of protamine insulin was given to a patient aged 28 years with diabetes of twelve months' duration who was admitted to the hospital in his first attack of severe diabetic acidosis. The carbon dioxide-combining power of the blood was 17 volumes per cent, and the sugar content was 288 mg per hundred cubic centimeters. No more insulin was given for twenty-four hours and, with the exception of rest in bed and careful nursing, no other treatment. In eighteen hours the sugar value was 72 mg, and the value for the carbon dioxide-combining power of the blood had risen to 32.4 volumes per cent. In this case, as in 2 cases described by Rabinowitch, there obviously was not a bad prognosis originally. The patient later was nicely stabilized with 30 units of protamine insulin daily.

In cases of greater severity diabetic acidosis demands a more vigorous attack, but even so the supplementary use of protamine insulin seems to be highly desirable. Recently at the Mayo Clinic it has been made a practice to give from 50 to 100 units without delay, the patient being treated thereafter in the conventional manner with such multiple doses of regular insulin as seemed to be required from examinations of the blood sugar and tests of fractional specimens of the urine. The relative promptness with which patients later can be stabilized on reasonably small doses of insulin has been impressive in the last 10 cases of diabetic acidosis in which patients were treated by this procedure. Similarly, insensitivity to insulin after a major surgical operation has been avoided to a great extent when protamine insulin was given before and after the operation.

Hypoglycemic Reactions Following the Administration of Protamine Insulin. The subject of reactions is unduly minimized in many of the reports on the use of protamine insulin. Reactions usually occur less frequently than with other forms of insulin, and the experienced patient, as a rule, is given a longer period of warning before the reaction becomes severe, although exceptions occur. I am informed of 1 death following the use of protamine insulin, and I fear that others will follow unless great pains are taken to impress patients with the importance of heeding early symptoms and combating them with carbohydrate. Muscular exertion is particularly likely to provoke reactions in a patient maintained with protamine insulin. This adds to the difficulty of treatment and demands either careful regulation of exercise or the administration of extra carbohydrate before and after unusual exercise.

The prodromes of reaction differ from those with which patients and physicians using regular insulin have become accustomed. Those symptoms which probably have been correctly attributed to the protective mobilization of epinephrine are less pronounced. The sugar level falls so gradually that the adrenal glands seem not to be aroused. Thus, tremor, sweating, tachycardia and a pounding pulse may be missing, and symptoms of cerebral origin, such as drowsiness, headache, nausea and fatigue, become the only criteria of hypoglycemia. This adds to the confusion, because such symptoms resemble those of diabetic acidosis. Vomiting has occurred in a number of cases, especially with reactions that occurred at night or were combated tardily. Those writing on the subject have emphasized the fact that reactions following the administration of protamine insulin are likely to be prolonged or to recur after treatment as more and more of the insulin suspension is dissolved and mobilized. It is well to tell the patient always to carry small cubes of loaf sugar with him or "life savers" (a fruit-flavored "life saver" weighs 2.5 Gm.) and to take one cube of sugar or one candy at the first

suggestion of any unusual symptom, and another every twenty or thirty minutes until the next meal if symptoms persist or recur

A severe reaction may be encountered after injections of protamine insulin. In several instances the patient has awakened in the morning with sore, stiffened muscles and a bitten tongue, and attacks with convulsions have been observed. Furthermore, long-continued hypoglycemia is not without peril, even if symptomless. I have referred to a study (fig 2) in which 70 units of insulin was given and food was withheld. The patient, a volunteer, was a vigorous young adult with diabetes. The sugar content remained in the neighborhood of 50 mg per hundred cubic centimeters for the last forty of the fifty-seven hours, but there were no symptoms (possibly because rest in bed was enforced) until the end of the period. The tendon reflexes then became exaggerated, and headache and mental confusion developed. The administration of dextrose relieved these abnormalities but not for several hours. Bollman³⁵ gave protamine insulin to dogs in sufficient doses to maintain long-continued hypoglycemia and, observing no symptoms other than drowsiness for fifty or sixty hours, then gave dextrose and found under those circumstances that fatal convulsions ensued. Animals that died during these attacks showed multiple petechial hemorrhages scattered throughout the brain.

Patients with Severe Diabetes Difficult to Treat Successfully The unstable diabetic patient continues to be unstable even when given protamine insulin. This is particularly true of patients with diabetes of great severity who have been treated for many years with regular insulin. Allen³⁶ commented on this in his discussion of papers by Campbell and Joslin. He stated that he selected intentionally a large proportion of cases of the most difficult diabetes in which the sugar level was most labile, and he was unable to obtain satisfactory regulation with protamine insulin, either alone or in conjunction with old insulin. Campbell,³⁷ in the same discussion, agreed that certain patients presented extreme difficulties but said that although it might take a longer time to attain a satisfactory balance in such cases, this had been accomplished in all his cases up to that time. In a number of cases of severe diabetes at the Mayo Clinic it has not been possible to maintain the urine continuously free from sugar without danger of reaction, and in such cases it has seemed to be safer to permit the intermittent excretion of some sugar. Even with this less satisfactory management the patients for the most part seemed to feel healthier and stronger than they had before. In some cases adjustment was difficult at first but later was not so

34 Footnote deleted by the author

35 Bollman, J. L. Personal communication to the author

36 Allen, F. M. *Tr. A. Am. Physicians* **51** 186, 1936

37 Campbell, W. R. *Tr. A. Am. Physicians* **51** 187, 1936

difficult Bertrand Smith also has had this experience and suggested "that a glycogenic function that has become somewhat adjusted to the more acute effect of regular insulin may be slow in adaptation to the more gradual effect of the protamine preparation"

The General Health of Patients Receiving Protamine Insulin Joslin,^{10b} Smith,¹³ Campbell³³ and several other clinicians have commented on the improved health of patients receiving protamine insulin Rabinowitch^{8b} observed a diminution in the bilirubin content of the serum In one group of cases the bilirubin was 1.26 mg before and 0.35 mg per hundred cubic centimeters after the new treatment was begun He found also that the cholesterol content of the blood was diminished in patients who showed any elevation of it on previous treatment with regular insulin Hanssen³⁸ reported that the enlarged (fatty?) livers of diabetic children and young adults diminished in size, and similar observations have been made by Winnett and Bowcock Joslin^{10b} and also Campbell³³ have expressed the hope that the degenerative complications of diabetes could be prevented by the uninterrupted action of insulin on patients treated with protamine insulin Priscilla White,³⁹ discussing recent progress in the treatment of severe diabetes, made the following comment

Whether one adheres to the theory that the high blood sugar or the high blood fat is responsible for complications in diabetes, the new preparation conquers both In all probability the severe diabetic who in 1950 will have survived fifteen years of the disease may present a picture quite different from that of the long duration diabetic whom we have presented today

Salt in the Treatment of Diabetes—In this review last year attention was directed to the observations of Glass and Beilless and those of McQuarrie and his colleagues, which MacLean and I were in part able to confirm, namely, that salts of sodium, particularly sodium chloride, reduce the requirement of diabetic patients for insulin A preliminary report by Sandstead⁴⁰ has just appeared, adding further confirmation and supplying the additional significant observation that ischemic pain and other neurocirculatory disturbances were affected to a strikingly satisfactory degree by treatment with salt Sandstead studied 8 diabetic subjects for periods of from two to twelve months Sodium chloride was given orally in doses of from 10 to 90 Gm daily, and in every instance it exerted a depressing effect on the sugar level of the blood and made it possible either to reduce the dose of insulin considerably

38 Hansen, P Enlargement of the Liver in Diabetes Mellitus, J A M A **106** 914-916 (March 14) 1936

39 White, Priscilla Recent Progress in Severe Diabetes, Canad M A J **35** 153-161 (Aug) 1936

40 Sandstead, H R The Effects of Oral Administration of Sodium Chloride in Diabetes, Hosp News **3** 1-11 (Nov 1) 1936

or to increase the diet or both. Ill effects were not demonstrable, and, contrary to a common belief that salt raises the blood pressure, the blood pressure was not raised in any instance. In 1 case of the type in which there was relative insensitivity to insulin, the dose of insulin was ultimately reduced from 124 to 35 units, without any other change in the diet.

The most important aspect of the report of Sandstead is that bearing on the influence of this treatment on neurocirculatory disturbances. Five patients had demonstrable arteriosclerosis, the diabetes had been present over periods varying between several months and several years. Four of these patients were complaining of the pain of diabetic neuritis, for which treatment in general has been very unsatisfactory. All were relieved of this pain, 1 in a few days, 1 in two weeks, 1 in three weeks and 1 in a month. It should be pointed out that the pain of diabetic neuritis often disappears more or less spontaneously in time. Nevertheless that 4 patients should find this degree of relief so promptly after beginning the treatment is of significance. A histamine flare test was made as a routine procedure on the legs as a means of determining the degree of capillary dilatability. In 1 of the 4 cases the test showed completely negative results before treatment as high as the knees, whereas a good response was obtained later as low as the feet.

Diagnosis of Diabetes—The diagnosis of diabetes ordinarily is not thought to present serious difficulties. The cardinal symptoms seen in the cases of more severe untreated diabetes often are pathognomonic, and the presence of reducing substances in the urine is suggestive in all cases and prompts further investigation. Exton⁴¹ maintained, however, that more mistakes are made than is supposed and that they are of two kinds: failure to make a diagnosis of diabetes and the making of a false diagnosis of diabetes mellitus. Whenever the test for reducing substances in the urine gives positive results, a determination should be made of the cause of the reduction, and if this is dextrose, a dextrose tolerance test should be made.

A new method of analyzing sugar quantitatively, which was used by Exton with six standard confirmatory methods, in reducing urine from 1,000 men and women, revealed that while dextrose caused 97 per cent of the 200 reductions in which the value, if expressed as dextrose, exceeded 1 per cent, it caused only 60 per cent of the 800 reductions in which the value was 1 per cent or less. As his experience had shown that 10 per cent of the cases in which dextrose was the reducing substance proved to be cases of renal or some other form of nondiabetic dextrosuria, it followed that only half the 800 specimens of urine con-

⁴¹ Exton, W. G. Differential Diagnosis of Conditions Associated with Sugar Excretion, New York State J. Med. **36** 1545-1553 (Oct. 15) 1936.

taining 1 per cent or less of reducing substances indicated the presence of diabetes

Analysis of the 400 cases in which the reduction was not from dextrose revealed interesting facts. In 73 per cent the reducing substances were multiple. In 13.8 per cent they could not be identified, in 7.1 per cent glycuronic acid was responsible, in 2.1 per cent pentose, in 1.8 per cent fructose, in 1.6 per cent vitamin C and in 0.6 per cent galactose. Recent employment of vitamin C in pharmaceutical form suggests that this will be found in the future more often than in the past. The figures for pentose and fructose bear out the supposition that pentosuria and fructosuria occur more frequently than is indicated in the literature. Other data of interest are included in the article and also a description of the "one-hour-two dose dextrose tolerance test" proposed by Exton as being simpler and more informative than the test for sugar tolerance usually performed.

Experience with Exton's simplified dextrose tolerance test has been favorable. It has now become a routine procedure at the Mayo Clinic, but my colleagues and I do not agree with Exton that it entirely avoids equivocal results, hence when the interpretation is doubtful, we repeat the examination, using a standard procedure. Also, we cannot agree with Exton when he insists that a dextrose tolerance test is indicated whenever the cause of the reduction of reducing urine is demonstrated to be dextrose. If the value for sugar in the blood is greater than 130 mg per hundred cubic centimeters in the morning before the ingestion of food, we regard the diagnosis of diabetes as established. The non-dextrose reducing substances found in urine do not provoke this degree of postabsorptive hyperglycemia. We reserve the dextrose tolerance test, therefore, for cases in which the sugar content of the blood in the morning is less than 130 mg per hundred cubic centimeters, thereby avoiding possible injury to patients who may have diabetes of greater severity than is immediately apparent.

Acidosis and Coma—Experience in the Mayo Clinic in 108 consecutive cases of severe diabetic acidosis was reported in this journal by Baker⁴². An interesting problem in connection with the subject is the nature and reason for the abdominal pain with spasm of the abdominal muscles, which so frequently leads to the fear, if not to an erroneous diagnosis, of an acute intra-abdominal disease. Walker⁴³ treated a patient with diabetic acidosis by giving 1,000 cc of a 0.9 per cent solution of sodium chloride together with 50 units of insulin. As frequently

42 Baker, T. W. A Clinical Survey of One Hundred and Eight Consecutive Cases of Diabetic Coma, *Arch Int Med* **58** 373-406 (Sept.) 1936.

43 Walker, Harry. The Etiology of Abdominal Pain in Diabetic Acidosis, *Ann Int Med* **9** 1178-1181 (March) 1936.

has been observed before, the severity of the abdominal pain began to lessen sooner than could be expected from any change produced by insulin. It lessened immediately, and within forty-five minutes had entirely disappeared. At the same time the abdomen lost its rigidity and became soft. Walker compared this observation to what is seen in heat cramps and gastric tetany. In both of them, as in diabetic acidosis, loss of chloride (and sodium) occurs. In heat cramps it results from perspiration, in gastric tetany, from vomiting and diuresis. In all three of these conditions spasm and pain affect muscles which are in action. In all of them relief from pain is promptly accomplished by restoring the lost electrolytes.

The same comments apply to the crisis of Addison's disease, in which loss of chloride and sodium also occur. Epigastric pain is an outstanding symptom and prompt relief usually is secured by administering intravenous injections of solution of sodium chloride. It appears that the pain in all these conditions may be attributed to the ischemia which results from the cramping of muscles and that the cramping is limited to actively contracting muscles. In diabetic acidosis and in Addison's disease the principal working muscles, aside from those of the heart, are those of respiration, and muscle spasm and consequent pain are limited usually to the muscles of respiration. This subject deserves more intensive investigation than has been devoted to it thus far.

Dillon, Riggs and Dyer⁴⁴ examined the brain in 8 fatal cases of uncomplicated diabetic coma and observed dilatation of the capillaries, perivascular edema, proliferation of the neuroglia and degeneration of the ganglionic cells. These abnormalities were most conspicuous in those parts of the brain which have been shown to be most susceptible to anoxemia produced by acute exsanguinating hemorrhage or by heart failure. Furthermore, the lesions were like those noted after acute asphyxia. In diabetic coma the total volume of the blood is reduced by hemoconcentration to a degree comparable to that in severe hemorrhage, and severe myocardial damage frequently accompanies it. Thus, it seemed to the authors that the abnormal physiology of diabetic coma is a reduced volume of circulating blood, a consequent marked reduction of blood pressure, both systolic and diastolic, limitation of the amount of blood flowing to the head and resulting anoxia of the brain. The cerebral lesions, in turn, may further embarrass the cardiac function by paralysis of the vasomotor and other vegetative centers, and in consequence the patient may die as a result of collapse of the vasomotor system or failure of the respiratory function, even when chemical estimation of the degree of acidosis indicates an improvement.

44 Dillon, E. S., Riggs, H. E., and Dyer, W. W. Cerebral Lesions in Uncomplicated Fatal Diabetic Acidosis, *Am J M Sc* **192** 360-365 (Sept.) 1936

Tuberculosis and Diabetes—The outlook for patients with diabetes complicated by tuberculosis is by no means as hopeless as has been supposed. Unfortunately, until recently, the staff physicians of many hospitals for tuberculous patients have not been prepared to provide expert control of the metabolic abnormality of these patients. Myers and McKean⁴⁵ in a small series of cases (80) obtained arrest or apparent arrest of tuberculosis in 21 per cent of the cases in which it was moderately advanced, in 25 per cent of those in class 3B and in 10 per cent of those in class 3C. Eventual arrest was anticipated in an additional 43 per cent of cases in class 2 and in another 16 per cent of those in class 3B. The results compared favorably with those for nondiabetic patients with tuberculosis of like severity in the same hospital. The tentative conclusion was reached that as long as the diet and insulin are regulated, coexisting diabetes does not have an adverse effect on the course of pulmonary tuberculosis. The average amount of insulin needed to bring the patients under control on admission was 46 units daily. The average dose at the time of dismissal was 42 units daily. The average diet contained 108 Gm of carbohydrate, 62 Gm of protein and 162 Gm of fat. In its relatively low amount of protein, its caloric content and its relatively high fat and carbohydrate ratio it was similar to that which McCann and Barr⁴⁶ found to be most suitable in cases of uncomplicated pulmonary tuberculosis.

A Public Health Problem—The increasing mortality among persons with diabetes is portrayed graphically in a recent bulletin of the Metropolitan Life Insurance Company⁴⁷. If the present trend is maintained, the relative positions of tuberculosis and diabetes as causes of death will be reversed within a decade. In one state, Nebraska, this has already occurred. In the four adjacent states (Iowa, Kansas and the Dakotas) the diabetes rate for 1933-1934 was close to that of tuberculosis, and in twelve of ninety-three cities of 100,000 population or more it was higher. Outstanding among communities in which this was found to be the case were Syracuse, N. Y., where the deaths among subjects with diabetes were 60.9 per cent in excess of those among subjects with tuberculosis, New Haven, Conn., with an excess of 43.7 per cent, and Rochester, N. Y., with an excess of 42.4 per cent. In the city of New York as a whole the deaths credited to diabetes were slightly less than half the total charged to tuberculosis, but in Brooklyn, N. Y., they were only

45 Myers, G. B., and McKean, R. M. Diabetes and Tuberculosis. I. An Analysis of Eighty Cases from the Standpoint of Tuberculosis, *Am Rev Tuberc* **32** 651-664 (Dec.) 1935.

46 McCann, W. S., and Barr, D. P., quoted by Myers and McKean⁴⁵.

47 The Comparative Mortality from Diabetes and Tuberculosis, *Stat Bull Metropolitan Life Ins Co* **17** 6-9 (Feb.) 1936.

31 per cent less. The implication of these figures is obvious. The subject will demand more and more attention from public health officials. The wise suggestion is made that groups which have been organized to combat tuberculosis extend their work to the study and control of diabetes and other chronic diseases. It is much better to use established agencies for this purpose than to create new ones, and the problems presented by diabetes from the point of view of control have many aspects in common with those of tuberculosis. This idea has already taken hold in several parts of the country and should be encouraged.

Theory of Diabetes—Sensitivity to Insulin. Attention was directed in an earlier review⁴⁸ to the studies of Faltz and his associates on the resistance to insulin encountered in some cases of diabetes. The subject has been studied also by several other investigators, and Himsworth, of London, and MacBryde, of St. Louis, have presented data of experiments that may affect therapeutic procedures. The observations of Himsworth⁴⁹ have appeared in British medical journals since 1932, they are summarized in his recent discussion before the Royal Society of Medicine. The extent to which the sugar content of the blood of healthy young men was lowered by a standard dose of insulin, administered by vein, was increased when the previous diet had been high in carbohydrate and decreased when the previous diet had been low in carbohydrate. These effects of a varying amount of dietary carbohydrate are not to be explained, he said, either by a difference in the reaction (p_H) of the tissues or by ketosis, and since the increased activity of insulin after carbohydrate feeding also was observed when the carbohydrate was given as dextrose by vein, it seemed unlikely that any hormone from the digestive tract, such as the "duodenin" described by Laughton and Macallum, could be a factor. Himsworth⁵⁰ thus reached the conclusion that the same dietetic factors which improve sugar tolerance in normal men also increase sensitiveness to insulin.

That more carbohydrate in the diet will increase and less carbohydrate will decrease the sugar tolerance of normal men was demonstrated independently by Adlersberg and Poiges⁵¹ and by Sweeney⁵²

48 Wilder, R. M., and Wilbur, D. L. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch. Int. Med.* **55**: 304-343 (Feb.) 1935.

49 Himsworth, H. P. Discussion of Physiological Factors Influencing the Action of Insulin, *Proc. Roy. Soc. Med.* **29**: 658-662 (April) 1936.

50 Himsworth, H. P. The Influence of Diet on the Sugar Tolerance of Healthy Men and Its Reference to Certain Extrinsic Factors, *Clin. Sc.* **1**: 251-264 (Nov. 14) 1934.

51 Adlersberg, D., and Porges, O. Zur Theorie und Praxis der kurativen Diabetesbehandlung, *Klin. Wchnschr.* **5**: 1451-1455 (Aug. 6), 1508-1513 (Aug. 13) 1926.

52 Sweeney, J. S. Dietary Factors That Influence the Dextrose Tolerance Test. A Preliminary Study, *Arch. Int. Med.* **40**: 818-830 (Dec.) 1927.

The interpretation of this, until recently, was that the higher tolerance after a high carbohydrate diet, as measured by dextrose tolerance tests and after preliminary injections of dextrose, was attributable to a greater sensitiveness of the pancreas, with a resultant more rapid or increased secretion of insulin. However, Dann and Chambers⁵³ showed that in dogs which had fasted for from fifteen to thirty days the administration of dextrose caused little rise in the respiratory quotient and that when insulin was injected at the same time, little more dextrose was oxidized. This demonstrated apparently that the diminished sugar tolerance after starvation (in which the metabolism is largely at the expense of fat) was not due merely to the lack of insulin. Important also in this connection is the work of Soskin,⁵⁴ to which reference was made in our last review. It does not disprove the previous contention that sugar stimulates a greater excretion of insulin, it suggests rather that more than one effect is produced.

Himsworth⁵⁵ showed further that the increased tolerance and increased activity of injected insulin, effected by feeding more carbohydrate to normal men, did not depend on the caloric value of the intake of food or on the ketogenic-antiketogenic ratio or on the fat content of the diet but rather on the absolute amount of carbohydrate. The quantitative nature of his experiments permitted the construction of curves to express the relationship of variation in the carbohydrate fed to change either in the dextrose tolerance or the sensitivity to insulin. He called these curves the "determination curve of glucose tolerance" and the "determination curve of insulin sensitivity." He found that the two had exactly the same form. He found also that when the change in the dextrose tolerance was plotted against the change in the sensitivity to insulin, a straight line was obtained, inclined 45 degrees to the horizontal, and from these observations he concluded that "the change in glucose tolerance consequent upon variation in the carbohydrate content of the diet is completely accounted for by change in the sensitivity to insulin secreted by the pancreas," thus excluding the necessity for assuming the secretion of more insulin by the pancreas.

Those readers who have had much experience with dextrose tolerance tests will remain skeptical as to whether blood sugar-time curves can safely be subjected to such precise mathematical analysis, and even granting that "the method of areas" employed by Himsworth is a step

53 Dann, M, and Chambers, W. H. Animal Colorimetry. Metabolism of Glucose Administered to Fasting Dog, *J Biol Chem* **89** 675-688 (Dec.) 1930

54 Soskin, S., Allweiss, M. D., and Cohn, D. J. Influence of the Pancreas and the Liver upon the Dextrose Tolerance Curve, *Am J Physiol* **109** 155-165 (July) 1934

55 Himsworth, H. P. The Dietetic Factor Determining the Glucose Tolerance and Sensitivity to Insulin of Healthy Men, *Clin Sc* **2** 67-94 (Sept 30) 1935

in the direction of accuracy of interpretation, it still may be doubted whether the results are as extremely accurate as Himsworth claimed. In any event, the case for relationship between the carbohydrate of the diet and the sensitivity to insulin is good and provides another explanation for the beneficial effects of diets high in carbohydrate in certain cases of diabetes. This provides also a rationale for treating diabetic coma with large doses of dextrose, as advocated by Ellis and referred to in an earlier review⁵⁶

Himsworth,⁵⁷ in 1934, showed with animals that the degree to which insulin suppressed hyperglycemia, produced by the administration of dextrose intravenously, was proportional to the sensitivity of the animal to insulin. By subjecting diabetic patients to this test he was able to distinguish two types of patient. In one, the "insulin-sensitive" type, injected insulin suppressed the hyperglycemia provoked by dextrose administered by mouth, in the other it failed to do so. The reaction of the "insulin-sensitive" diabetic patient to dextrose and insulin was like that obtained in healthy subjects, but the reaction of the "insulin-insensitive" diabetic patient was abnormal. In the former, hyperglycemia was prevented, in the latter it was not.

Himsworth's inquiry then was directed to discover why the action of insulin was impaired in the type of diabetic patient insensitive to insulin and to determine whether this impairment was due to derangement of hepatic function or to inhibition of the action of insulin in the periphery. For this purpose comparison was made of the content of sugar in arterial blood (blood flowing freely from the lobe of the ear) and that in blood drawn simultaneously from a vein. This co-called arteriovenous difference normally was moderately increased when dextrose was administered to normal subjects, and when insulin was given with the dextrose the arteriovenous difference amounted to as much as 30 or 40 mg per hundred cubic centimeters of blood. With diabetic patients of the "insulin-sensitive" type, the response to this test was like that of normal subjects, whereas with those of the "insulin-insensitive" type, the response was minimal, indicating inhibition of the peripheral action of insulin. Soskin and his associates,⁵⁴ although agreeing with Himsworth that the pancreas does not secrete an increased amount of insulin after the injection of dextrose, disagreed with him in attributing importance to the activity of insulin in the periphery. They considered that differences between the values found for sugar in arterial and in venous blood are of no significance unless they first are corrected for rate of blood flow and hydration.

56 Wilder, R. M., and Wilbur, D. L. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch. Int. Med.* **57**: 422-471 (Feb.) 1936.

57 Himsworth, H. P. Diabetes Mellitus. Its Differentiation into Insulin-Sensitive and Insulin-Insensitive Types, *Lancet* **1**: 127-130 (Jan. 18) 1936.

In any case, Himsworth⁵⁷ was led to suggest that the diabetes of the "insulin-sensitive" type of patient was attributable to lack of insulin, whereas that of the "insulin-insensitive" type of patient was due not to lack of insulin but to insensitivity to insulin. This he correlated with the observed action of carbohydrate on sugar tolerance. "Insulin-sensitive" patients tolerated large increases in dietary carbohydrate without requiring an increased dose of insulin, but "insulin-insensitive" patients showed glycosuria after only slight increases in the dietary carbohydrate. "The insulin-sensitive diabetic thus apparently reacts like the normal subject by becoming more sensitive to insulin as the dietary carbohydrate increases, whilst giving more carbohydrate administered to the insulin-insensitive does not evoke this reaction."⁴⁹

Himsworth⁴⁹ has offered two explanations of this variability of sensitiveness to insulin. He first assumed that an activator was involved, an insulin kinase, the action of which was complementary to that of insulin. Later, the studies of Marks,⁵⁸ to be referred to presently, suggested to Himsworth the view that the variation may be accounted for by the presence of more or less of some antagonist to insulin.

MacBryde's⁵⁹ study of a group of diabetic patients led to the conclusion at which Himsworth arrived, namely, that diabetic patients fall into two types, one sensitive to insulin and the other relatively insensitive. The distinguishing criteria differed, however. He tested the response to an injection of 1 unit of insulin for each 10 pounds (4.5 Kg.) of body weight and found that some patients showed a marked fall in the sugar content of the blood, whereas others showed relatively little response. He also tested the tolerance to overdoses of insulin and observed that those patients showing sensitivity by the first test would tolerate little or no increase in the dose of insulin above the daily requirement, whereas those who were resistant according to the first test could tolerate large overdoses, in some cases as much as 60 units or more. He tested also the number of grams of dextrose metabolized per unit of insulin and found in patients sensitive to insulin that this ranged from 1 to 3 Gm., whereas in those insensitive to insulin it was less than 0.5 Gm. MacBryde's patients who were sensitive to insulin, however, failed to gain tolerance with a higher carbohydrate diet, there being only 1 exception among 8 patients, whereas his "insulin-insensitive" patients (he used the term "insulin resistant")

⁵⁸ Marks, H. P. The Pituitary Factor, *Proc. Roy. Soc. Med.* **29** 663-666 (April) 1936.

⁵⁹ MacBryde, C. M. Response to Insulin as an Index to the Dietary Management of Diabetes, *J. Clin. Investigation* **15** 577-589 (Sept.) 1936, *Advances in the Dietary Management of Diabetes*, *South. M. J.* **29** 488-491 (May) 1936.

gained tolerance on a high intake of carbohydrate. This is exactly opposite to what Himsworth⁵⁷ observed, and thus what seemed to promise a means of harmonizing the clinical practice of those advocating a diet high in carbohydrate and those recommending a diet high in fat only adds to the existing confusion.

The position of those clinicians who are adhering to a course between the extremes of a diet high in fat and a diet high in carbohydrate seems to be supported by Himsworth's⁵⁵ "insulin sensitivity determination curve," to which I have referred. This curve shows that in a normal subject a rise in sensitivity to insulin and consequently an improvement in the ability of the body to dispose of carbohydrate occur as the dietary carbohydrate is increased from 50 to 200 Gm a day but that little increase in sensitivity occurs when the dietary carbohydrate is increased beyond 200 Gm until the amount of 350 Gm is exceeded, when another but more moderate increase of sensitivity is observed. In other words, the best effectiveness of insulin and the maximal disposal of dietary carbohydrate by each unit of insulin seem to be obtained when the diet contains 200 Gm of carbohydrate. Below this allowance further addition of carbohydrate demands a proportionately small increase of insulin, whereas above this allowance a relatively larger increase of insulin is needed. Himsworth seemed to lay less emphasis on the significance of this "insulin sensitivity determination curve" than I have, at least I am led to judge so by the fact that he advocated the use of a diet containing much more than 200 Gm of carbohydrate. He even stated the opinion that a diet in which the carbohydrate represents less than 50 per cent of the total calories may cause progressive permanent impairment of sugar tolerance, so that in the course of time diabetes mellitus results.

Himsworth has published two articles on statistics regarding diabetes in support of this contention. In one of these he and Marshall⁶⁰ attempted to show that most diabetic patients selected a diet low in carbohydrate before diabetes developed. In the other⁶¹ he pointed to a correlation between the dietary habits of persons in various communities and countries and the diabetic mortalities. These statistical articles are not good. The difference between the diets of diabetic patients before they had diabetes and of the group of nondiabetic patients is slight, and the difference between the amount of carbohydrate included in diets in certain states of the United States with a high incidence of diabetes and in others with a lower incidence also is not enough to impress any one who does not wish to believe that this is the explana-

60 Himsworth, H. P., and Marshall, E. M. The Diet of Diabetics Prior to the Onset of the Disease, *Clin. Sc.* **2** 95-115 (Sept. 30) 1935.

61 Himsworth, H. P. Diet and the Incidence of Diabetes Mellitus, *Clin. Sc.* **2** 117-148 (Sept. 30) 1935.

tion For instance, the death rate from diabetes in the state of Maine was 25.5 per hundred thousand, whereas that of the adjacent province of Quebec was 11, that of the United States as a whole was 20, and that of Canada as a whole was 12. It may be true that the inhabitants of the United States eat more fat and therefore less carbohydrate than do people in Canada, but Himsworth's own experiments show that differences in carbohydrate consumption between the gross values of 200 and 350 Gm. are of little consequence in the sensitivity of healthy subjects to insulin (their own insulin). The sharp slopes of his "insulin sensitivity determination curve" occur, as I have stated, when the amount of carbohydrate is changing from 50 to 200 Gm., and when it exceeds 350 Gm. It is doubtful whether many persons, either in Maine or in Quebec, eat less than 200 Gm. or more than 350 Gm. of carbohydrate a day.

There are far too many inestimable factors to justify any conclusion today as to why diabetes is so unequally distributed over the world, or as to why there is so much more diabetes (death from diabetes) in the northern tier of states of the United States than in the southern tier or in the provinces of Canada. A factor which seems more important than the difference in the consumption of carbohydrate by these respective populations is that disclosed by the observations of Petersen⁶² and, independently, those of Mills⁶³. This, namely, is a correlation between the incidence of death with diabetes and the frequency and severity of changes in the weather (temperature, barometric pressure, humidity, ionization of air and so forth). The northeastern and north central states of the United States are in the track of the major cyclonic disturbances. These storms acquire their greatest severity as they sweep eastward from Montana to the northeast. The weather of the Canadian provinces is much less affected by them, and the states south of the Ohio River lie south of this storm track.

The Rôle of the Hypophysis in Carbohydrate Metabolism—I have mentioned that Himsworth seemed to be prepared to abandon his early assumption of an insulin activator (kinase) in favor of an inhibitor and that he has been influenced in this by the results of investigations by Marks⁵⁸. Marks, with Best, Dale and Hoyt, confirmed the observation of Mann and Magath that sugar disappears from the blood in animal preparations when the influence of the liver is excluded and

62 Petersen, W. F., and Milliken, M. E. *The Patient and the Weather. The Footprint of Asclepius*, Ann Arbor, Mich., Edwards Brothers, Inc., 1935, vol. 1, pt. 1, *Autonomic Integration*, 1936, vol. 1, pt. 2, *Autonomic Dysintegration*, 1934, vol. 2.

63 Mills, C. A. *Health and Disease as Influenced by Climatic Environment*, *Internat. Clin.* 2: 143-167 (June) 1936, *Diabetes Mellitus. Is Climate a Responsible Factor in the Etiology?* *Arch. Int. Med.* 46: 569-581 (Oct.) 1930.

that injections of insulin accelerate the rate of this disappearance. They could account quantitatively for the sugar, it was mainly stored in the muscles as glycogen. In the intact animal when the blood sugar falls after an injection of insulin, it is restored again by the conversion of hepatic glycogen into dextrose in response to stimulation of the liver by epinephrine. This has been demonstrated repeatedly. It now appears that if the hypophysis is removed from the animal, the percentage of sugar produced in the blood by a small dose of insulin is not corrected, the sugar content continues to fall until the animal dies in convulsions. This occurred, as was demonstrated by the experiments of Cope and Marks,⁶⁴ even when the liver was abundantly supplied with glycogen, as well as under conditions in which the compensatory secretion of epinephrine was found to take place just as it does in a normal animal. The conclusion followed that the absence of the hypophysis leads to a greater stability of hepatic glycogen. Supportive evidence was provided by experiments on the perfused livers of hypophysectomized frogs. In them glycogen was converted into sugar much less readily than in a normal animal.

The converse of this ineffective recovery from hypoglycemia of an animal deprived of its hypophysis also was observed. An abnormally intense secretion of dextrose by the liver, coupled with an exaggerated phase of recovery from hypoglycemia, followed injections of insulin when suitable extracts of the anterior lobe of the pituitary gland were injected. But apart from any action on the liver, these extracts of the anterior lobe also inhibited or delayed the peripheral action of insulin, as judged by observations on the arteriovenous differences of the sugar contents.

Marks⁵⁸ commented on the striking resemblances between these effects of extracts of hypophysis and those observed (by Himsworth) when the diets of normal subjects and diabetic patients contained varying amounts of carbohydrate. Marks, therefore, was led to suggest that the anterior lobe of the hypophysis is stimulated by an inadequate supply of carbohydrate. He suggested that the hypophysis is concerned in the production of carbohydrate from protein or fat or both and that the greatest demand is made on it when the organism, because of lack of available carbohydrate, is forced to obtain its necessary dextrose from protein or fat. Thus, when the diet is poor in carbohydrate, the hypophysis is stimulated, and the peripheral response to insulin is inhibited, and vice versa, when the diet is rich in carbohydrate, the hypophysis becomes inactive, the peripheral response to insulin is no longer inhibited and at the same time dextrose is less easily mobilized from the liver.

64 Cope, O, and Marks, H. P., quoted by Marks⁵⁸

In a previous review⁴⁸ (1935), when discussing the work of H Locke, whose experiments led him to conclude that the hypophysis exerts its influence on carbohydrate metabolism by way of the central nervous system, I commented on the demonstration on cats by Davis and his associates that experimental lesions accurately placed in the hypothalamus would permit removal of the pancreas without the development of severe diabetes. The lesions were produced bilaterally by means of the Horsley-Clarke stereotaxic instrument. If Locke's observations were correct, it seemed to me that these cats should be resistant to injections of extracts of the anterior lobe of the hypophysis containing the blood sugar-raising (contra-insular) agent, and if this were found to be the case it would do much to establish the reliability of Locke's conclusions. This experiment has now been performed by Ingram and Barris⁶⁵. Four of a group of 5 cats with lesions located in the supra-chiasmatic portion of the hypothalamus and including the filiform nuclei, failed to show normal responses to the blood sugar-elevating effect of a suspension of the anterior lobe of the hypophysis. The preparation caused hyperglycemia in normal cats. Three other cats manifested retarded responses to the action of much smaller doses. That the failure to respond actively to the suspension of the anterior lobe of the hypophysis was not due to a deficient supply of hepatic glycogen was established by removing samples of liver from the animals at the end of the periods of observation. The values for glycogen ranged from 3.09 to 5.51 per cent.

Ingram and Barris⁶⁵ expressed the opinion that the effect of lesions of the hypothalamus on carbohydrate metabolism could be interpreted in either of two ways: (1) that the site of action of the diabetogenic (contra-insular) hormone of the anterior lobe of the hypophysis was destroyed or (2) that injury to the hypothalamus had depressed the action of the anterior lobe of the hypophysis. Houssay had objected to Locke's conclusion that hormones of the anterior lobe of the hypophysis act by way of the hypothalamus, basing his criticism on the results of experiments on toads. Although Houssay and Biasotti⁶⁶ had found that lesions in the hypothalamus prevented or ameliorated diabetes, they had ascribed this result to the loss of some direct nervous influence on the anterior lobe of the hypophysis. Ingram and Barris refrained from drawing final conclusions. However, they pointed out that nerve connections between the hypothalamus and the anterior lobe

65 Ingram, W. R., and Barris, R. W. Evidence of Altered Carbohydrate Metabolism in Cats with Hypothalamic Lesions, *Am J Physiol* **114** 562-571 (Feb.) 1936.

66 Houssay, B. A., and Biasotti, A. Hypophysektomie und Pankreasdiabetes bei der Krote, *Arch f d ges Physiol* **227** 239-250, 1931.

of the hypophysis, if there are any at all, are not well established and that the evidence that some hypothalamic lesions appear to depress the diabetogenic activity of active suspensions of the anterior lobe of the hypophysis supported the assumption of Locke that the site of action of the diabetogenic hormone is in the hypothalamus. They stated that the frequency with which bilateral atrophy or destruction of the filiform nuclei was associated with alteration of carbohydrate metabolism was striking but that exceptions occurred (in 1 cat in which these cell groups were destroyed the response to the hyperglycemic activity of suspensions of the anterior lobe of the hypophysis was entirely normal) and therefore that the matter of more exact localization of the areas concerned must await further study.

The idea that diabetes mellitus depends on uncontrolled activity of the anterior lobe of the hypophysis is supported by the fact that injections of an estrogenic substance alleviate to some extent the symptoms of diabetes in depancreatized dogs (Barnes, Regan and Nelson, 1933). This has been observed also in some instances of diabetes mellitus by Mazer, Meranze and Israel⁶⁷ and Houssay⁶⁸ but was not found by Collens and his associates⁶⁹. Also, de Wesselow and Griffiths⁷⁰ recently have reported that injections of blood plasma from a particular type of diabetic patient rendered rabbits less sensitive to insulin, much as would an injection of extract of the anterior lobe of the pituitary gland. The possibility was entertained that this type of diabetic patient corresponds to the "insulin-insensitive" type of Himsworth.

In this connection Young⁷¹ offered the following contribution. Mention has been made of the observation by Cope and Marks that injection into rabbits of a saline suspension of the anterior lobe of the pituitary gland was followed by resistance to the action of insulin and increased sensitivity to the hyperglycemic effect of epinephrine. Young⁷² investigated the factor responsible for these effects and found it to be closely associated, if not identical, with the lactogenic hormone. Incidentally, the lactogenic hormone is now being considered as iden-

67 Mazer, Meranze and Israel, quoted by Young⁷¹

68 Houssay, B. A., quoted by Young⁷¹

69 Collens, W. S., Slo-Bodkin, S. G., Rosenbliett, Sidney, and Boas, L. C. The Effect of Estrogenic Substance on Human Diabetes, *J. A. M. A.* **106** 678-682 (Feb. 29) 1936

70 deWesselow, O. L. V., and Griffiths, W. J. On the Possible Rôle of the Anterior Pituitary in Human Diabetes, *Lancet* **1** 991-994 (May 2) 1936

71 Young, F. G. Glycogen and the Metabolism of Carbohydrate, *Lancet* **2** 237-242 (Aug. 1), 297-302 (Aug. 8) 1936

72 Young, F. G. The Influence of Anterior Pituitary Extracts on the Glycaemic Response to Insulin and Adrenaline in Rabbits, *J. Physiol.* **87** 13P-15P (March 14) 1936

tical with the adrenotropic hormone, which brings these observations into line with those of Long and Lukens,⁷³ to which reference will be made presently. Further exploration of this interesting possibility is awaited with interest. The period of lactation is a time when sugar is withdrawn from the blood at an accelerated rate, hypoglycemia threatens and sometimes develops in cows that are bred to produce milk abundantly. The association in one factor of a stimulant to lactation with an action on the liver and periphery, which increases the discharge of sugar from the former and diminishes utilization by the latter, would be highly purposeful.

Collip⁷⁴ has suggested that the diabetogenic action of extracts of the anterior lobe of the hypophysis is due to the combined effect of two substances, one acting on the level of the blood sugar and the other producing ketosis. Young⁷¹ said he thought it possible that three substances are concerned: (1) a factor which stimulates the formation of glycogen in the liver and which may be associated with the ketogenic factor, (2) a glycotropic factor, which facilitates hepatic glycogenolysis and inhibits to some extent the peripheral action of insulin and (3) a glycogenolytic factor, causing hyperglycemia. Any of these alone is not diabetogenic, but their combined action would result in an increased production of sugar in the liver, ketosis and possibly in decreased utilization of sugar in the periphery. Hertz⁷⁵ has called attention to a possible relationship between von Gierke's disease and the hypophysis. This condition is characterized by the excessive formation of hepatic glycogen accompanied with ketonuria, and it would result from the first of the three factors mentioned. The extracts prepared by Young inhibited the action of insulin but did not produce ketosis or affect the level of the sugar in the blood during fasting. This is the second factor, the third presumably is a hormone producing more intense excretion of sugar by the liver. It seems rather unreasonable thus to multiply the number of hormones in the hypophysis, in time the observations probably will be explained more simply than this.

⁷³ Long, C. N. H. The Interrelationships of the Glands of Internal Secretion Concerned with Metabolism, *Am J M Sc* **191** 741-759 (June) 1936, Disturbances of the Endocrine Balance and Their Relation to Diseases of Metabolism, *Ann Int Med* **9** 1619-1627 (June) 1936. Long, C. N. H., and Lukens, F. D. W. The Effects of Adrenalectomy and Hypophysectomy upon Experimental Diabetes in the Cat, *J Exper Med* **63** 465-490 (April) 1936, The Effect of the Adrenotropic Fraction of the Anterior Pituitary upon the Glycosuria of Hypophysectomized-Depancreatized Cats, *Am J Physiol* **116** 96, 1936, The Effect of Adrenalectomy upon the Fatty Infiltration of the Liver Following Total Pancreatectomy in the Cat, *ibid* **116** 96-97, 1936.

⁷⁴ Collip, J. B., quoted by Young⁷¹

⁷⁵ Hertz, W., quoted by Young⁷¹

Significant as this newer work on the physiology of carbohydrate metabolism appears to be, clearly there is much to be learned before the results can be interpreted clinically. Woodyatt,⁷⁶ it is true, found that the administration of an extract of the anterior lobe of the hypophysis to diabetic patients might cause an increase of glycosuria. After the high dose was interrupted an improvement might occur comparable to that which follows removal of the hypophysis of animals with pancreatic diabetes. This is what should be expected. Acromegaly in its stages of activity frequently, but by no means always, is associated with (provokes?) diabetes. Clinical insufficiency of the anterior lobe of the hypophysis should increase the tolerance for sugar, and there is some evidence that it does (Goetsch, Cushing and Jacobson⁷⁷), although a number of cases of hyperglycemia and glycosuria have been reported in patients with hypopituitarism, the last one being reported by Sexton and Neuhoff⁷⁸. The diabetes was considered to be "of true pancreatic origin" by Sexton and Neuhoff, that is, "due to a deficiency in insulin," and its occurrence was considered to be "entirely independent of the pituitary syndrome." In my opinion in the large majority of cases diabetes is independent of any abnormality of the pituitary gland.

The Rôle of the Adrenal Glands in Carbohydrate Metabolism—The observation of Buell, Strauss and Andrus⁷⁹ that lactic acid is produced only slowly by the autolyzing muscles of adrenalectomized rats, although the lactic acid content of the blood is known to be high in such animals led them to the assumption that glycogenesis from lactic acid may occur less readily when the influence of the adrenal glands is removed. Other experiments support this assumption⁸⁰. Known amounts of lactic acid neutralized with sodium hydroxide were given by stomach tube to (1) normal rabbits, (2) adrenalectomized rats insufficiently treated with adrenal cortex extract, (3) adrenalectomized rats treated only with salt solution and (4) adrenalectomized rats adequately treated with the cortical extract. The livers of each of the rats deprived of its adrenal glands and inadequately treated with adrenal cortex extract or treated

76 Woodyatt, R. T. *Tr. A. Am. Physicians* **51** 123-127, 1936.

77 Goetsch, Emil, Cushing, Harvey, and Jacobson, Conrad. *Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri. An Experimental and Clinical Study*, *Bull. Johns Hopkins Hosp.* **22** 165-190 (June) 1911.

78 Sexton, D. L., and Neuhoff, Fritz. *Pituitary Infantilism with Diabetes Mellitus*, *Endocrinology* **20** 856-859 (Nov.) 1936.

79 Buell, Strauss and Andrus, quoted by Buell, Anderson and Strauss⁸⁰.

80 Buell, Mary V., Anderson, I. A., and Strauss, Margaret B. *On Carbohydrate Metabolism in Adrenalectomized Animals*, *Am. J. Physiol.* **116** 274-281, (July) 1936.

only with salt contained much less glycogen than the livers of normal rats subjected to identical conditions. At the same time the blood of these animals contained several times as much lactic acid as was found in the blood of normal rats, in spite of the fact that the amount of lactic acid absorbed from the bowel was in many cases less than that in the normal animals. In adrenalectomized rats adequately treated with adrenal cortex extract the liver was well supplied with glycogen, although the blood of these animals contained somewhat more lactic acid than was found in the blood of the normal rabbits. Thus, there appears to be another function of the liver under the regulation of the cortex of the adrenal glands. The analogous clinical disturbance should be looked for in Addison's disease. Possibly a test for this disease might be based on the rate at which a given dose of lactate is disposed of by the patient. In diabetic acidosis lactic acid tends to accumulate together with the keto-acids. Perhaps this may indicate that in severe acidosis the function of the adrenal glands is depressed. Certainly it is a fact that the amount of sugar excreted by a diabetic patient often diminishes after acidosis has developed. The sugar content of the blood is correspondingly decreased, and Evans⁸¹ has proposed that the adrenal cortex has to do with the ability of the liver to convert protein into carbohydrate.

Reference has been made in previous reviews to the experiments of Long and Lukens⁷⁸ on cats from which both the pancreas and the adrenal glands were removed. These animals were treated with adequate doses of adrenal cortex extract and salt and survived for from two to four weeks. During this time they manifested as little evidence of diabetes as do animals after hypophysectomy. Particularly noticeable was the suppression of ketosis. The cortex rather than the medulla was thought to be necessary for the maintenance of the diabetic state in the depancreatized animals, because cats from which only the medulla of the adrenal glands and at a later date the pancreas were removed did not show any amelioration of the diabetic condition. Rather strangely, the administration of adrenal cortex extract prepared by the method of Swingle and Pfiffner did not aggravate the diabetes, as might be expected, even when large doses were given. This extract apparently does not contain that factor of the intact cortex of the adrenal gland which acts in carbohydrate metabolism, or at least does not contain much of it. Confirmation and extension of these observations, both with dogs and with cats, has been provided by Berg, Gross,

⁸¹ Evans, Gerald. The Adrenal Cortex and Endogenous Carbohydrate Formation, *Am J Physiol* **114** 297-308 (Jan) 1936

Lowenberg and Zucker⁸² Their study indicated in their opinion that the adrenal gland as a part of an emergency reflex mechanism to prevent hypoglycemia is not required but that a factor derived from the cortex is necessary In the adrenalectomized animal, in the absence of a naturally stored substance or of injected adrenal cortex extract, a sugar content of the blood depressed by insulin is not restored spontaneously, as is usual The dose of extract in these experiments was from 2 to 5 dog units per kilogram per day, from two to five times the requirement for maintenance

Long and Lukens⁷³ reported this year that an adrenotropic fraction of the anterior lobe of the hypophysis injected into cats from which both the hypophysis and the pancreas previously had been removed markedly increased the excretion both of dextrose and of nitrogen The extract was obtained from Dr Collip Similar effects were obtained in cats both after feeding and after fasting, even when the animals were not exhibiting glycosuria at the time the injections were made The volume of urine excreted usually was doubled The amount of dextrose could be accounted for on the assumption that it was derived from the protein represented by the nitrogen Equivalent amounts of the same extract injected into hypophysectomized and depancreatized cats from which the adrenal glands also had been removed was without effect The interpretation given by the authors was that hypophysectomy probably results in this effect on experimentally produced diabetes by reason of the accompanying hypofunction of the adrenal cortex, but it is recognized that this is not proved If this view is correct, the adrenal cortex must contain at least two hormones, one that appears to control the metabolism of sodium (or potassium) and another, at present a hypothetical entity, the function of which is particularly concerned with the production of dextrose from protein (and possibly with certain aspects of the metabolism of fatty acids and lactic acid) As yet no one has demonstrated the ability of extracts of the adrenal cortex to accentuate diabetic conditions in adrenalectomized and depancreatized animals, and until such time as this is accomplished the possibility still exists that adrenalectomy effects pancreatic diabetes by altering the normal secretory activity of the anterior lobe of the hypophysis

Long and Lukens have successfully performed experiments involving astonishing technical difficulties At several meetings during 1936 they have shown moving pictures illustrating cats that survived successfully and were maintained for many days with salts and adrenal cortex

82 Berg, B N , Gross, J , Lowenberg, C , and Zucker, T F The Adrenal Medulla and Cortex in Relation to Effects of Insulin, *Arch Path* **22** 283 (Aug) 1936 Houssay, B A , and Biasotti, A Influencia de la hipofisis y la suprarenal sobre la diabetes pancreatica del sapo, *Rev Soc argent de biol* **12** 104-111 (June) 1936

extract after removal of the hypophysis, the pancreas and both adrenal glands. The period of survival and the good general condition of these animals permitted more satisfactory studies of metabolism than have been possible heretofore on adrenalectomized animals.

Fatty Degeneration of the Liver in Pancreatic Diabetes—Long and Lukens⁷³ observed in cats that fatty infiltration and degeneration of the liver followed total pancreatectomy, even though enough insulin was provided to control the diabetes. However, in cats that previously had been either hypophysectomized or adrenalectomized, this disturbance of the liver did not occur. Denervating the adrenal glands or removing only the medulla did not prevent it, and from this they presumed that the adrenal cortex was responsible for the fat in the liver and the degeneration of the liver that usually characterize pancreatic diabetes and that this action of the adrenal glands depended on the presence of the hypophysis.

The observation that animals (depancreatized dogs) adequately treated with insulin undergo fatty infiltration and degeneration of the liver and then die was made by the first investigators to use insulin experimentally.⁸³ The disturbance could be prevented by feeding raw pancreas to these diabetic animals, and later Best⁸⁴ showed that feeding lecithin, choline or betaine also would prevent the disturbance. An important observation was reported this year by Dragstedt, Van Prohaska and Harms⁸⁵. These investigators confirmed the fact that the removal of the pancreas caused the fatty disease of the liver in question and that it was not due to the absence of pancreatic juice. It was not observed in normal dogs with a complete pancreatic fistula or in dogs after the pancreatic ducts had been ligated, and administration of active pancreatic juice was not of any avail. From 100 to 1,100 cc of fresh pancreatic juice was administered daily without benefit, but it was found that 25 Gm of fresh beef pancreas fed daily would both prevent or cure the abnormality and permit survival of the animal. Ten grams of fresh beef pancreas was not sufficient, and boiled pancreas was ineffective. An extract from fresh beef pancreas was made, and its admin-

83 Allan, F. N., Bowie, D. J., MacLeod, J. J. R., and Robinson, W. L. Behavior of Depancreatized Dogs Kept Alive with Insulin, *Brit J Exper Path* **5** 75-83 (April) 1924.

84 Best, C. H., Ferguson, G. C., and Hershey, J. M. Choline and Liver Fat in Diabetic Dogs, *J Physiol* **79** 94-102 (July 28) 1933.

85 Dragstedt, L. R., Van Prohaska, John, and Harms, H. P. Observations on a Substance in Pancreas (a Fat Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, *Am J Physiol* **116** 36-37 (June) 1936, The Relation of Pancreatic Juice to the Fatty Infiltration and Degeneration of the Livers of Depancreatized Dogs, *ibid* **116** 122-123 (June) 1936.

istration prevented fatty infiltration and degeneration of the liver and cured the disturbance after it had developed. The extract was fat free, and thus its action could not be attributed to lecithin. Nor was it due to choline, because doses of choline that were several times as large were ineffective. The active derivative of the pancreas was prepared by extracting the pancreas with 95 per cent alcohol, afterward evaporating the alcohol filtrates at room temperature, drying the residue and washing it several times with several volumes of ether. The product was effective when administered orally in amounts corresponding to 100 Gm of beef pancreas.

The clinical bearing of fatty degeneration of the liver in pancreatic diabetes and its prevention by the various means suggested are not immediately apparent. Diabetes in man seldom depends either on complete destruction of the pancreas or on suppression of its external secretion, and, so far as I know in the few cases in which this may be true, fatty degeneration of the liver has not been demonstrated. In 2 cases in which diabetes was associated with lesions of the pancreas resulting in steatorrhea recently studied at the Mayo Clinic by Barger, Bollman and Kepler,⁸⁶ no clinical evidence could be obtained of disturbed function or other abnormality of the liver. On the other hand, a large (fatty?) liver is seen occasionally in cases of diabetes mellitus in which the external function of the pancreas apparently is intact. Hansen,⁸⁸ as has been mentioned, reported a number of instances of this abnormality in young diabetic patients but found in every case that the liver diminished in size after a period of treatment with protamine insulin. This suggests that the discontinuous action of insulin, when readily soluble (regular) insulin is given by infrequent injection, may be responsible for the hepatic degeneration of depancreatized animals and that pancreas and derivatives of pancreas given by mouth could owe their curative and preventive properties to some action whereby a more continuous insulin effect is maintained.

Fatty degeneration of the liver grossly similar to that obtained in diabetic animals has been reported by Judd, Kepler and Rynearson⁸⁷ in cases of severe chronic hypoglycemia. Two patients were subjected to exploratory operations, and specimens of the liver were removed for histologic examination. No tumor (insular adenoma) could be found. These patients were not benefited by treatment with choline or betaine.

⁸⁶ Barger, J. A., Bollman, J. L., and Kepler, E. J. "Diarrhea of Diabetes" and Steatorrhea of Pancreatic Insufficiency, *Proc. Staff Meet., Mayo Clin.* **11** 737-742 (Nov. 18) 1936.

⁸⁷ Judd, E. S., Kepler, E. J., and Rynearson, E. H. Spontaneous Hypoglycemia. Report of Two Cases Associated with Fatty Metamorphosis of the Liver, *Am. J. Surg.* **24** 345-363 (May) 1934.

Glyconeogenesis—Among the evidence frequently quoted as supporting the theory of glyconeogenesis from fatty acids is that presented by Chaikoff and Weber⁸⁸ They injected epinephrine into depancreatized dogs during fasting and recovered from the urine a larger amount of dextrose than they could account for on the assumption that the only endogenous source of dextrose is from protein, the glycerol of fat and the glycogen present in liver and muscle Bollman, Mann and Wilhelmj,⁸⁹ repeating this work, determined the glycogen content before and after injecting epinephrine and reported that the "extra glucose obtained was equal to the amount of glycogen removed from the muscle" Bachrach, Bradley and Ivy⁹⁰ again have repeated the experiment, conducting it exactly as originally described by Chaikoff and Weber and using Chaikoff and Weber's values for the maximal amount of glycogen to be found in the liver and muscle of depancreatized dogs

Tabulation of Results, Adapted from Bachrach, Bradley and Ivy

Observers	Number of Dogs	Pre Epinephrine Dextrose-Nitrogen Ratio	Nitrogen Excreted During Epinephrine Period, Gm per Kg	Dextrose Excreted During Epinephrine Period, Gm per Kg	Extra Dextrose in Epinephrine Period, Gm per Kg
Chaikoff and Weber	7	6.5	0.41	4.9	3.1
Bollman, Mann and Wilhelmj	4	3.2	0.39	2.2	1.2
Bachrach, Bradley and Ivy	14	2.4	0.41	2.4	1.8

after three days of fasting All the dextrose excreted under the influence of epinephrine could be accounted for without postulating the formation of any dextrose from fat

The accompanying table shows that the discrepancy between the results of Chaikoff and Weber and those of the later investigators is largely contributed to by the dextrose-nitrogen ratio for the period immediately preceding the administration of epinephrine The average dextrose-nitrogen ratio for this period obtained by Chaikoff and Weber was extraordinarily high (6.5) The amounts of nitrogen found by all the observers were similar, and the differences all lie in the amount of dextrose excreted This indicates that the animals of Chaikoff and

88 Chaikoff, I. L., and Weber, J. J. The Formation of Sugar from Fatty Acids in the Depancreatized Dog Injected with Epinephrine, *J Biol Chem* **76** 813-832 (March) 1928

89 Bollman, J. L., Mann, F. C., and Wilhelmj, C. M. The Origin of Glucose Liberated by Epinephrine in Depancreatized Animals, *J Biol Chem* **93** 83-91 (Sept.) 1931

90 Bachrach, W. H., Bradley, W. B., and Ivy, A. C. Effect of Epinephrine on Glucose Excretion in Fasted Depancreatized Dogs, *Am J Physiol* **117** 203-205 (Oct.) 1936

Weber had not reached a fasting level and that stored glycogen was contributing a larger share of the extra dextrose than they estimated. Thus honors still rest with Minkowski in this never ending controversy as to whether diabetes depends on the deficient utilization or the excessive formation of sugar.

Exercise and Carbohydrate Tolerance—Courtice and Douglas⁹¹ studied the effects of long walks on the metabolism of 2 subjects (themselves), the standard exercise being 10 miles (16 kilometers) at a rate of 4½ miles (7 kilometers) per hour. They observed that the respiratory quotient showed a rise in the early stages of the walk, enough to account for a consumption of 100 Gm of carbohydrate. During the rest that followed the walk it fell to average figures, between 0.76 and 0.73, it remained low for three hours and in one experiment for nine and a half hours. This was accompanied with moderate ketosis, which had not appeared during the walk. A diet high in carbohydrate when given the day before the experiment prevented such ketosis, but giving more carbohydrate the morning of the exercise and a normal diet the day before did not. The respiratory quotient never fell so low as to afford indubitable evidence of the formation of sugar from fat.

In the rest period after exercise in these studies the sugar content of the blood never fell below normal limits, but the injection of sucrose, dextrose or fructose gave evidence of a reduced tolerance for sugar. It was therefore concluded that the function of the endocrine organs associated with carbohydrate metabolism may be correlated with the varying activity of the muscles and so afford a partial explanation of the changes in carbohydrate metabolism which result from severe exercise.

Dehydration in Diabetes—Formerly it was assumed that the dehydration of diabetes could be attributed exclusively to glycosuria. When the concentration of dextrose in the blood exceeded a given threshold value, sugar was excreted by the kidneys and carried water with it. Certainly this was shown to occur, indeed, extreme dehydration could be produced when solution of dextrose was injected by vein into normal dogs at a rate exceeding the rate of utilization. This information was obtained from an elaborate series of experiments performed years ago by Woodyatt and his associates. More recently, as more came to be known about the rôle of ions of sodium in the metabolism of water, the loss of water in diabetic acidosis came to be explained on the basis of ketonuria. The ketones, being acids, are eliminated as salts of sodium, and loss of water follows the loss of base. Now, Himwich and Faze-

91 Courtice, F. C., and Douglas, C. G. The Effects of Prolonged Muscular Exercise on the Metabolism, *Proc. Roy. Soc., London*, sB **119** 381-439 (March 2) 1936.

kas⁹² have reported experiments showing that the dehydration in diabetes may occur without ketonuria. Partly depancreatized dogs were given carbohydrate, fat and protein in amounts sufficient to maintain caloric equilibrium and insulin in doses adequate to prevent glycosuria. The protein content and the total base of the serum and the oxygen capacity of the blood, as well as the nitrogen, dextrose, total base and ketone content of the urine, were determined. Then the amount of dextrose in the diet was increased enough to produce glycosuria uncomplicated by ketonuria. The animals sustained a loss of weight associated with an increase in the volume of urine and a loss of base in the urine. That the loss of weight was due to dehydration could be told by the increased protein content of the serum and the raised capacity for oxygen of the blood. Subsequently, after an increase in the amount of sodium chloride in the diet the body was rehydrated as the deficit of sodium was corrected. Thus, although the mechanism of dehydration in diabetes may depend primarily on glycosuria, the importance of the part played by sodium is again emphasized.

HEMOCHROMATOSIS

The literature contains only a few scattered references to estimations of the iron content of the blood in cases of hemochromatosis, none being more recent than 1921. The technics employed have been improved. Therefore, the determinations made by Sachs, Levine and Griffith⁹³ are important. Their studies of the blood of 200 normal men and women, using the method of Wong, indicated for the men an average content of 50 mg of iron per hundred cubic centimeters, with a range of from 40.05 to 58.6 mg and a probable error of 2.56 mg. The figures for women were lower, showing a range from 33.45 to 49.25 mg, with an average of 42.67 mg and a probable error of 2.13 mg per hundred cubic centimeters. In 3 cases of hemochromatosis in men (1 doubtful as to diagnosis) the values for iron ranged from 88.9 to 74.4 per cent of these average figures. The copper content of the blood exceeded the normal average by from 9.8 to 18.2 per cent. This increase for copper was within the normal range and in view of the small number of cases was not thought to be significant.

⁹² Himwich, H. E., and Fazekas, J. F. A Mechanism of Dehydration in Diabetes, *Am J Physiol* **116** 75-76 (June) 1936.

⁹³ Sachs, Adolph, Levine, V. E., and Griffith, W. O. Blood Iron and Copper in Hemochromatosis, *Proc Soc Exper Biol & Med* **35** 332-335, 1936.

Book Reviews

Exploration radiologique des colons et de l'appendice au moyen des solutions floculantes Images de muqueuses By George Mangot, Raymond Sarsin and Henri Dulcos Price, 200 francs Pp 229, with 203 illustrations Paris Masson & Cie, 1935

From a roentgenologic study of the colon and appendix much valuable information can be obtained regarding these organs which could not be obtained in any other manner In order to enhance the value of such a study, it is necessary to employ the correct technic in examining these organs and to have a clear understanding of the normal roentgenologic appearance of these organs and the variations within the normal

This monograph, prefaced by an excellent dissertation by Dr Antoine Bécléré, eminent French roentgenologist, clearly explains the modern methods employed in examining the colon and appendix by means of the roentgen rays The authors explain the roentgen aspects of the anatomy and physiology of the colon and appendix Their study of the intestinal mucosa by means of colloidal thorium dioxide injected into the bowel is most interesting After the injection of this opaque medium the colon is examined (1) under pressure, (2) after the elimination of most of the medium and (3) after the injection of air They believe that there is a precipitation of the thorium dioxide on the mucosa of the intestine and that in this manner certain features of the mucosa are brought out in relief which could not be obtained in any other manner Thorium, a radio-active element, owing to its high atomic number and specific density has a high absorbability rate for the roentgen ray In the form of the dioxide it has been used in visualizing the hemoptic and lymphatic systems, and it has been used also in ventriculography and urography

The authors have divided their book into four parts the first part deals with technic, the second with symptomology, the third with syndromes and the fourth with the appendix The chapter on the appendix is especially interesting and instructive Those who still believe that the roentgen rays can offer little in the diagnosis of a chronic disorder of the appendix will profit greatly by reading this chapter, and only the most skeptical will fail to become convinced of its usefulness in this regard

There is an extensive bibliography appended which represents the work of the best known roentgenologists of Europe and America Singularly, however, the master of them all has been left out, namely, the late Russell Carmen, of the Mayo Clinic The authors could have profited much by consulting the numerous works which Carmen published on the gastro-intestinal tract

The book, which is easy to read and contains numerous beautiful illustrations, represents much labor and skill in its construction

Experimental Studies on a Transmissible Myelomatosis (Reticulosis) in Mice By Otto Kaalund-Jørgensen Translated into English by Robert Fraser Price, 12 kroner Pp 142, with 25 illustrations Copenhagen Levin & Munksgaard, 1936

This monograph combines an excellent review of the literature concerning leukotic conditions in mice and guinea-pigs and the results of extensive and thorough experiments by the author It has been fairly well established in the literature that leukosis in fowls can be transmitted by cell-free filtrable agents and that transmissible leukosis and filtrable sarcoma of fowls have many properties in common Mammalian leukosis has, however, been transmitted only by means of living cells The overwhelming majority of the transmissible mammalian leukoses hitherto described either have been or have been conceived as being lymphatic Only in the last year or so (Furth and others) have reports appeared showing the existence of transmissible myeloid leukosis in mammals The author's experi-

ments are concerned with the transmissibility of myeloid leukosis (myelomatosis). The use of mice of genetically pure strains is important for successful transmission. However, insusceptibility to implantation of leukotic cells can in many cases be overcome by general exposure of the animal to roentgen rays previous to inoculation. This makes it possible to use mice of unrelated strains. The author has succeeded in transmitting myelomatosis from mice to irradiated rats. His proof of the impossibility of transmitting myeloid leukemia by cell-free agents is convincing. It is shown that myelomatosis can be transmitted by an extremely small number of cells (about eight) and that the disease becomes systemic a short time after inoculation. The determination of the lethal roentgen dose for myelomatosis (3,100 to 3,700 roentgens) and the description of the technic and roentgen dose used for increasing the susceptibility of mice to transmissible leukosis are valuable. The neoplastic nature of mammalian leukosis is well supported, and the author believes that all human leukosis may well be due to neoplastic processes in the hematopoietic system.

There are twenty-four excellent photomicrographs in this book, the one colored plate might have been omitted. Robert Fraser, the English translator of this work, is to be congratulated, as are also the publishers. This monograph is indispensable to any one interested in experimental leukosis.

An Index of Treatment By various writers, edited by Robert Hutchinson, M D. Eleventh edition. Price, \$12. Pp 1035, with 147 illustrations. Baltimore. William Wood & Company, 1936.

The first edition of this index appeared in 1907, and evidently the work has since had a successful life of twenty-nine years, for new editions have been forthcoming at appropriate intervals in an effort to keep it up to date. American medical men, on the whole, have not been too enthusiastic over it. In the book's early days, for example, *The Journal of the American Medical Association* (50:2148 [June 27] 1908) greeted it coldly. "The work is intended to provide the practitioner with a complete guide to treatment, and the services of a large number of eminent authors whose names carry weight with English-speaking physicians have been made use of. The result is as satisfactory as a book constructed on this plan can well be." The reviews of subsequent editions have been equally lukewarm.

On the other hand, in England the "Index" appears to be more generally liked. The *British Medical Journal* has recently said of the latest edition: "During nearly three decades this well known source of reference has gained an established hold in confidence on the profession. Once again Dr Robert Hutchinson must be warmly congratulated on his critical acumen as editor and on his success in literature and medicine. The Index is assured of continuing popularity."

One gathers, therefore, that there is a difference of opinion on the two sides of the Atlantic regarding the value of a compendium of this kind. Admittedly, it is well put together, with articles written by distinguished clinicians, and well edited. As a textbook of treatment, however, most American teachers will continue to look askance at it and to describe it, a little superciliously, as being "as satisfactory as a book constructed on this plan can well be."

The Specificity of Serological Reactions By Karl Landsteiner, M D. Price, \$4. Pp 178. Springfield, Ill. Charles C. Thomas, Publisher, 1936.

This modest book is a most commendable and systematic presentation and discussion of the basic factors of immunity and resistance. The author has kept consistently to fundamentals and has analyzed them in clear terms. This is the first concise analysis of the work that has been done on the basis of the present knowledge of the chemical specificity of the fundamental factors of the immunologic Trinity—the antigen, the binding substance and the substrate. The evidence is reviewed that proves "that serologic properties are intimately connected with chemical constitution." The bibliography of the basic research and the index make this small book a necessary and useful reference tool for workers in the field of immunology.

INTAKE OF POTASSIUM, AN IMPORTANT CONSIDERATION IN ADDISON'S DISEASE

A METABOLIC STUDY

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It has long been recognized that injections of sodium chloride are of benefit in the treatment of the characteristic crises of Addison's disease, but it was the quantitative investigation of the electrolytes of the plasma by Loeb and his associates¹ and by Harrop and his associates² that first revealed why large amounts of sodium and chloride are required effectively to combat such crises. Their experiments demonstrated that the loss of ions of sodium and chloride is one of the principal disturbances leading to the development of the crisis and that the crisis can be prevented by a quantitative replacement of these ions. However, the results obtained by treating patients only with sodium chloride have remained less satisfactory than those obtained when extract of adrenal cortex has been given, and no one has succeeded in maintaining indefinitely the life of a completely adrenalectomized dog by administering only sodium chloride. Thus, for some time it has been evident that the

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Read before the Association of American Physicians, Atlantic City, N J, May 5, 1936. An abstract was printed in the Proceedings of the Staff Meetings of the Mayo Clinic (**11** 273-283 [April 29] 1936)

1 Loeb, R F , Atchley, D W , Benedict, Ethel M , and Leland, Jessica. Electrolyte Balance Studies in Adrenalectomized Dogs with Particular Reference to Excretion of Sodium, *J Exper Med* **57** 775-792 (May) 1933

2 Harrop, G A , Soffer, L J , Ellsworth, Read, and Trescher, J H. Studies on Suprarenal Cortex. III Plasma Electrolytes and Electrolyte Excretion During Suprarenal Insufficiency in the Dog, *J Exper Med* **58** 17-38 (July) 1933

course of Addison's disease is influenced unfavorably by factors other than the supply of sodium chloride

The next step was the identification of one of these other factors by Harrop and his associates³ and simultaneously by Allers and one of us (D. I. Kendall),⁴ working independently. This, namely, is the requirement of more ions of sodium than of chloride. Harrop observed that the excretion of sodium was greater than the excretion of chloride if sodium chloride alone was given to adrenalectomized dogs and that while neither sodium chloride nor sodium bicarbonate would maintain the lives of such animals, the simultaneous administration of these salts would do so. Allers and Kendall, attempting to maintain adrenalectomized dogs with sodium chloride alone, made the observation that the alkali reserve of the blood fell to low levels, and they suspected that acidosis was responsible for the failure of these animals to survive. The urea content of the blood, which usually is markedly elevated in conditions of severe adrenal insufficiency, was not elevated in animals receiving large amounts of sodium chloride, and when the acidosis was corrected by supplying extra base, as sodium in the form either of sodium bicarbonate or of sodium citrate, the dogs remained in excellent condition for indefinite periods.

The probable bearing of these observations on the successful treatment of Addison's disease was emphasized for us by the discovery of a patient who, in addition to having a spontaneous craving for salt, such as frequently occurs in Addison's disease, which she satisfied by eating salt, took generous quantities of sodium bicarbonate because of pyrosis. She had preserved her weight and strength without other treatment for five years. The results obtained, however, by treating other patients with sodium bicarbonate or sodium citrate and sodium chloride remained less satisfactory than was desirable. Patients would do well for weeks or months and then, for no apparent reason, would fail and would require injections of extracts of adrenal cortex. Thus, other uncontrolled factors still remained unrecognized.

Although the results obtained by Harrop and his co-workers and by Kendall and Allers⁵ were similar in regard to the necessity for administering extra sodium ion with sodium chloride, they were not similar

3 Harrop, G. A., Soffer, L. J., Nicholson, W. M., and Strauss, Margaret. Studies on Suprarenal Cortex. IV. The Effect of Sodium Salts in Sustaining the Suprarenalectomized Dog, *J. Exper. Med.* **61** 839-860 (June) 1935.

4 Allers, W. D. Influence of Diet and Mineral Metabolism on Dogs After Suprarenalectomy, *Proc. Staff Meet., Mayo Clin.* **10** 406-409 (June 26) 1935. Allers, W. D., Nilson, N. W., and Kendall, E. C. Studies on Adrenalectomized Dogs. The Toxic Action of Potassium, *ibid.* **11** 283-288 (April 29) 1936.

5 Kendall, E. C., Mason, H. L., Myers, C. S., and Allers, W. D. A Physiologic and Chemical Investigation of the Suprarenal Cortex, *J. Biol. Chem.* **114** 1411-1431, 1936.

in regard to the maintenance of the normal level of electrolytes in the blood. The former authors stated that "it is only by the exhibition of both extract and salt in adequate amounts that entirely normal plasma electrolyte levels may be sustained in the totally suprarenalectomized dog." They did not attempt to give a diet which was either low or uniform in its content of potassium. The adrenalectomized dogs treated by Kendall and Allers with sodium chloride and sodium citrate were given a diet with an unusually low content of potassium. Under these conditions not only could the animals be maintained indefinitely without the use of extracts of adrenal cortex, but the level of the electrolytes in the plasma also remained entirely normal. Furthermore, adrenalectomized dogs maintained only with sodium chloride and sodium bicarbonate or citrate without the use of extract of adrenal cortex were found to be surprisingly sensitive to small amounts of potassium in the diet. If 0.5 Gm of potassium was added to the daily diet of such dogs, a state of crisis was produced like that of acute adrenal deficiency. This occurred even when the animals were receiving liberal supplies of the sodium salts named.⁶

A preliminary observation in a case of Addison's disease seemed to indicate that patients similarly are sensitive to the addition of potassium to their diet. The following investigation was therefore undertaken to determine (1) whether higher intakes of potassium would consistently provoke substantial losses of sodium and chloride and thus favor the development of symptoms of crisis and (2) whether restricting the intake of potassium might be advantageous in the maintenance of patients with Addison's disease, in particular whether such restriction might lessen the requirement for sodium salts and extract of adrenal cortex.

PROCEDURE

Three patients were chosen for investigation, two of them had previously been the subjects of metabolic observations, and symptoms of crisis had developed on withdrawal of sodium chloride from the diet. All revealed the characteristic pigmentation and other typical symptoms of Addison's disease. They were placed in the hospital under close supervision, and special care was exercised to make complete collections of the urine, this being further controlled by daily determinations of the excretion of creatinine.

Constant diets were served, planned so that their content of ions of sodium approximated 0.59 Gm, of chloride 0.91 Gm and of potassium 1.6 Gm, except that in period 2 in case 3 (table 3) the food was made to contain 5.8 Gm of potassium. The composition of the diets in sodium, chloride and potassium

⁶ Confirmation of these observations by experiments performed on cats and rats has appeared in a paper by Zwemer and Truszkowski (Science **83** 558-560 [June 5] 1936) since the preparation of this manuscript.

was estimated from the tables of Sherman⁷ The levels of intake of sodium, chloride and potassium were increased in various periods by the addition to the diet or the administration separately of weighed amounts of the salts of these substances

ANALYTIC METHODS

Urine—The various constituents of urine were determined by the following analytic methods

Nitrogen Macro-Kjeldahl

Chloride Volhard

Sodium Gravimetric determination of sodium as sodium zinc uranyl acetate, using the method of Barber and Kolthoff,⁸ as modified by Butler and Tuthill⁹

Preformed creatinine Folin¹⁰

Total creatinine Folin, the urine being boiled with trinitrophenol

Potassium Fiske and Litarczek¹¹ and Folin¹²

The Fiske and Litarczek method of analysis for potassium is based on a preliminary precipitation of potassium as potassium cobaltinitrite and final precipitation as potassium bitartrate The following precautions and slight modifications proved to be of value Extreme care was necessary in washing the precipitate of tartrate to insure complete removal of the excess of tartaric acid from the precipitate The alcohol was allowed to pass through the filter pads at a rate of about 1 cc in three or four minutes Instead of transferring the filter pads after the final precipitation, the precipitated tartrate was removed by allowing hot water to pass slowly through the filter pads so that the potassium bitartrate was completely dissolved This permits the use of the same filter pads for a series of determinations A more dilute solution of sodium hydroxide (0.005 to 0.01 normal) was used for the final titration, and the solution was stirred during titration with air freed from carbon dioxide An 0.02 per cent solution of phenol red was used as the indicator Under these conditions, with a solution of purified potassium chloride containing from 2 to 4 mg of potassium, the average recovery of potassium was 99.6 per cent The data reported were obtained both from ashed and from unashed samples, with, in general, excellent duplication of

7 Sherman, H. C. Chemistry of Food and Nutrition, ed 3, New York, The Macmillan Company, 1926, p 587

8 Barber, H. H., and Kolthoff, I. M. A Specific Reagent for the Rapid Gravimetric Determination of Sodium, J Am Chem Soc **50** 1625-1631 (June) 1928, Gravimetric Determination of Sodium by the Uranyl Zinc Acetate Method II Application in the Presence of Rubidium, Cesium, Potassium, Lithium, Phosphate or Arsenate, *ibid* **51** 3233-3237 (Nov) 1929

9 Butler, A. M., and Tuthill, Elizabeth. An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, J Biol Chem **93** 171-180 (Sept) 1931

10 Folin, Otto. On the Determination of Creatinine and Creatine in Urine, J Biol Chem **17** 469-473, 1914

11 Fiske, C. H., and Litarczek, George. A New Method for Potassium, J Biol Chem **67** xvi-xvii, 1926

12 Folin, Otto. Laboratory Manual of Biological Chemistry, ed 5, New York, D Appleton-Century Company, Inc, 1934, pp 177-179 and 239

results If, however, the specimens of urine had been made acid with sulfuric acid to prevent a loss of nitrogen, satisfactory results could be obtained only by ashing the samples before the analysis was made If hydrochloric acid had been used, ashing was not necessary, although in all cases a preliminary evaporation of the sample was made in order to remove the excess acid

Blood Serum—The following analytic methods were used for blood serum

Sodium Butler and Tuthill's modification of Barber and Kolthoff's method

Chloride Open Carius method as applied by Van Slyke¹³

Potassium A dry sodium cobaltinitrite reagent was prepared according to the method of Fiske and Litarczek The determinations were made of extracts of serum ashed in the muffle, with the precautions necessary to avoid loss of potassium and sodium The potassium was precipitated as sodium potassium cobaltinitrite, according to the conditions of Fiske and Litarczek but omitting digestion with nitrohydrochloric acid The precipitate was centrifugated, and the potassium was titrated with potassium permanganate, according to the method of Kramer and Tisdall¹⁴

PROTOCOLS

CASE 1—Observation as to the Effect of the Level of Intake of Potassium on Addison's Disease—The subject of this study was a woman 39 years of age who, except for minor ailments, was well until August 1933 She then began to lose weight and strength and observed increasing pigmentation of the skin In August 1934 she became suntanned, and the tan never faded After April 1935 the pigmentation became deeper, and weakness increased to such an extent that the patient took to her bed She recently had been treated with injections of a commercial extract of adrenal cortex¹⁵ and for several months had of her own accord been taking extra sodium chloride by mouth because of a marked craving for it She first came to the clinic and was admitted to the hospital on Nov 11, 1935

Examination revealed diffuse pigmentation of the skin and mucous membranes, associated with many black freckles The systolic blood pressure in millimeters of mercury was 92 and the diastolic 64 Roentgenograms revealed no evidence of tuberculosis of the lungs and no calcification in the region of the adrenal glands The flocculation test for syphilis was negative The values for the sodium chloride in and for the carbon dioxide-combining power of the blood were normal The value for blood urea also was normal

Observations from November 15 to December 2 (metabolic data in table 1 and chart 1, period 1) On November 15 the daily intake of potassium was lowered to an amount not greater than 16 Gm This was accomplished by suitably adjusting the diet For the next ten days 12 Gm of extra sodium chloride was administered daily by mouth, making a total intake of about 18 Gm of sodium chloride Five grams of sodium citrate also was given daily Adrenal cortex

13 Van Slyke, D D The Determination of Chlorides in Blood and Tissues, *J Biol Chem* **58** 523-529 (Dec) 1923

14 Kramer, Benjamin, and Tisdall, F F A Clinical Method for Quantitative Determination of Potassium in Small Amounts of Serum, *J Biol Chem* **46** 339-349 (April) 1921

15 The preparation used was eschatin

extract¹⁶ was withheld. The condition of the patient remained very good, in fact, it was distinctly better than at the time of her admission to the hospital. She was able to get up from bed and to be around in the halls of the hospital every day. She slept well and ate practically all the food that was served to her.

TABLE I

Date	Lot	Amount, Cc	Intake								Twenty Four Hour Urine										Pot. gms	
			Extract of Adrenal Cortex	Sodium Chloride, Gm	Sodium Citrate, Gm	Total Sodium		Total Chloride		Total Potassium		Total Nitrogen, Gm	Volume, Cc	Creatinine Nitrogen, Gm	Total Nitrogen, Gm	Creatinine Nitrogen, Mg	Sodium		Chloride			
						Gm	Millimols	Gm	Millimols	Gm	Millimols						Gm	Millimols	Gm	Millimols		
Nov '935																						
15				18.0	5	8.07	350	11.00	308	1.6	41	6.2										
16				18.0	5	8.07	350	11.00	308	1.6	41	6.7	2,140	0.29	6.60	35	7.40	324	9.61	240	140	1.40
17				18.0	5	8.07	350	11.00	308	1.6	41	5.9	1,250	0.26	5.06	42	5.23	228	6.40	180	106	1.06
18				18.0	5	8.07	350	11.00	308	1.6	41	5.6	1,310	0.27	4.65	25	5.89	256	7.47	210	114	1.14
19				18.0	5	8.07	350	11.00	308	1.6	41	6.6	745	0.21	3.31	11	2.82	123	3.29	91	0.65	0.65
20				18.0	5	8.07	350	11.00	308	1.6	41	6.9	1,460	0.25	3.70	3	4.27	186	4.79	130	0.73	0.73
21				18.0	5	8.07	350	11.00	308	1.6	41	6.7	1,465	0.29	4.28	5	4.29	187	5.00	140	0.91	0.91
Period 1—Effect of Restricting Intake of Sodium																						
22				18.0	5	8.07	350	11.00	308	1.6	41	6.6	1,145	0.30	4.75	1	5.21	226	6.64	187	1.91	1.91
23				18.0	5	8.07	350	11.00	308	1.6	41	6.7	1,070	0.18	2.82	1	3.89	169	5.11	144	0.66	0.66
24				18.0	5	8.07	350	11.00	308	1.6	41	6.6	1,660	0.29	4.73	7	6.15	268	8.14	228	1.18	1.18
25				6.0		2.37	103	3.65	103	1.6	41	6.6	1,380	0.27	4.34	16	5.40	235	6.86	193	0.81	0.81
26				6.0		2.37	103	3.65	103	1.6	41	6.9	1,545	0.29	4.60	9	3.48	151	4.53	128	0.65	0.65
27				1.5		0.59	26	0.91	26	1.6	41	6.6	1,400	0.27	4.33	12	2.64	115	3.17	89	0.51	0.51
28				1.5		0.59	26	0.91	26	1.6	41	6.9	1,100	0.28	4.50	9	2.45	107	2.94	83	0.51	0.51
29				1.5		0.59	26	0.91	26	1.6	41	6.7	990	0.27	4.48	19	2.01	88	2.48	70	0.50	0.50
30				1.5		0.59	26	0.91	26	1.6	41	5.9	735	0.24	4.62	21	1.55	68	1.89	53	0.51	0.51
Dec																						
1				1.5		0.59	26	0.91	26	1.6	41	6.4	895	0.27	4.72	44	1.17	51	1.54	43	0.90	0.90
2				18.2	2	7.59	330	11.10	313	1.6	41	3.7	875	0.29	4.65	78	0.88	38	1.08	31	0.56	0.56
3				16.0	5	7.27	317	9.75	275	1.6	41	4.6	1,040	0.25	4.69	75	2.10	91	3.44	97	1.44	1.44
4				16.0	5	7.27	317	9.75	275	1.6	41	5.8	1,245	0.28	4.96	68	3.30	144	4.93	138	1.42	1.42
5				16.0	5	7.27	317	9.75	275	1.6	41	4.6	1,320	0.24	3.58	30	3.47	150	4.33	122	1.36	1.36
6				16.0	5	7.27	317	9.75	275	1.6	41	6.7	1,160	0.20	2.77	16	2.79	122	3.20	90	0.91	0.91
7	52	10		16.0	5	7.27	317	9.75	275	1.6	41	6.4	1,750	0.29	4.03	9	4.09	178	4.78	130	1.46	1.46
8	52	10		16.0	5	7.27	317	9.75	275	1.6	41	6.7	1,073	0.26	4.17	3	3.67	160	4.22	119	1.25	1.25
9				16.0	5	7.27	317	9.75	275	1.6	41	6.6	1,073	0.26	4.17	0	3.67	160	4.22	119	1.25	1.25
10				16.0	5	7.27	317	9.75	275	1.6	41	4.8	1,340	0.26	4.07	7	5.22	227	6.16	176	0.99	0.99
11				16.0	5	7.27	317	9.75	275	1.6	41	4.1	1,387	0.27	3.77	0	5.11	222	6.49	183	0.91	0.91
12				16.0	5	7.27	317	9.75	275	1.6	41	6.7	1,387	0.27	3.77	1	5.11	222	6.49	183	0.91	0.91
13				16.0	5	7.27	317	9.75	275	1.6	41	6.6	1,380	0.30	4.03	15	3.73	162	4.69	182	0.91	0.91
14				16.0	5	7.27	317	9.75	275	1.6	41	6.6	1,400	0.29	3.71	12	4.03	175	5.10	143	0.77	0.77
Period 2—Effect																						
15				16.0	5	7.27	317	9.75	275	1.6	41	6.6	1,495	0.29	3.23	18	3.37	147	4.45	125	0.95	0.95
16				16.0	5	7.27	317	9.75	275	4.0	102	6.6	1,800	0.29	3.27	21	4.59	191	5.68	160	0.91	0.91
17				16.0	5	7.27	317	9.75	275	4.0	102	6.7	2,060	0.27	3.14	13	6.82	297	8.44	231	1.70	1.70
18				6.0		2.37	103	3.65	103	4.0	102	6.6	1,984	0.26	3.16	5	5.54	241	7.04	198	1.53	1.53
19				6.0		2.37	103	3.65	103	4.0	102	6.9	1,984	0.26	3.16	5	5.54	241	7.04	198	1.53	1.53
20	52	20		26.0	10	12.19	529	15.85	445	4.0	102	6.7	2,055	0.26	3.36	2	6.47	281	8.12	229	2.76	2.76
21				16.0	5	7.27	317	9.75	275	4.0	102	6.6	2,150	0.30	4.86	11	7.84	341	9.26	261	4.18	4.18
22				16.0	5	7.27	317	9.75	275	4.0	102	5.4	1,570	0.26	4.00	35	5.55	242	7.11	200	2.45	2.45
23				6.0		2.37	103	3.65	103	4.0	102	5.8	2,030	0.27	3.95	11	5.12	223	6.52	183	2.19	2.19
24				26.0	10	12.19	529	15.85	445	4.0	102	6.9	2,060	0.28	4.21	14	4.41	192	6.00	169	2.46	2.46
25				16.0	5	7.27	317	9.75	275	1.6	41	6.6	1,410	0.29	4.40	13	4.20	183	4.60	130	2.43	2.43
26				11.0	2.5	4.83	210	6.72	189	1.6	41	6.9	1,300	0.31	4.36	29	4.74	206	6.03	170	1.69	1.69
27				11.0	2.5	4.83	210	6.72	189	1.6	41	6.4	1,100	0.31	3.48	17	3.17	138	4.34	122	0.98	0.98
28				11.0	2.5	4.83	210	6.72	189	1.6	41	6.4	1,140	0.27	2.80	14	2.96	129	4.06	116	0.93	0.93
29				11.0	2.5	4.83	210	6.72	189	1.6	41	6.4	1,420	0.29	3.12		3.25	141	4.69	134	1.17	1.17

¹⁶ Except when otherwise specified, the extract of adrenal cortex administered in these cases was cortin prepared in the laboratory of the Division of Biochemistry of the Mayo Foundation.

On November 25 the extra sodium salts were withheld. This reduced the intake of sodium chloride to about 6 Gm a day, namely, to the salt naturally contained in the food and the 4.5 Gm of sodium chloride used in seasoning the food. On November 27 the sodium chloride used as seasoning was omitted,

data in Case 1

Blood Plasma								Blood Pressure, Mm of Mercury		Clinical Observations	
Sodium		Chloride		Potassium, Mg per 100 Cc	Urea, Mg per 100 Cc	Sugar, Mg per 100 Cc	Carbon Dioxide, Vol per 100 Cc	Body Weight, Kg	Systolic		Diastolic
Mg per 100 Cc	Millimols per Liter	Mg per 100 Cc	Millimols per Liter								
317	138	375	106		24	80	61	60.7	78	50	Began diet low in potassium
306	133	377	107			85	57	60.0	84	56	
								60.0	82	54	
314	137	375	106		24	76	58	60.0	68	54	Occasional nausea Stronger No change
315	137	374	106	15.7				60.0	90	64	
								59.5	90	62	
319	139	371	105	18.2	18	75	57	59.3	88	60	
Chloride, with Intake of Potassium at a Low Level											
								60.2	84	70	Stronger No change
324	141	376	106	15.8	18	76	55	60.2	78	56	
									70	54	
322	140	371	105	16.3	18	91	52	60.1	80	64	Weaker Weaker, sleepless
								59.5	68	54	
324	141	374	106	16.3	18	77	49	60.0	78	68	
316	137	363	102	17.2	21			58.6	80	62	Weaker Weaker, sleepless
309	134	354	100	17.9	24	88	52	57.9	80	55	
								57.7	88	76	
299	130	343	97	20.4	24	97	57	57.7	72	50	Nausea, slept well Very weak, sleepless
298	129	337	95	19.8	27	106	51		86	52	
306	133	365	103	19.9	36	90	49	58.4	86	58	
								58.6	85	56	Stronger
								59.0	88	55	
								59.1	76	42	
								59.1	84	42	Hiccup, still weak Remains weak Much stronger
								59.5	80	52	
314	137	388	109		18	74	50	60.0	72	54	
								59.9	78	56	Low abdominal cramps Menstruation began Stronger
									78	42	
								59.3	80	64	
								59.1	80	64	Much improved As well as on entry No change
								59.1	80	62	
Increasing Intake of Potassium											
								59.9	74	48	Doing well No change No change
								59.7	78	48	
								59.1	72	62	
335	146	383	110	18.5	14	80	53	59.5	74	52	No change Much weaker Very sick
325	141	381	109	18.3	14	88	50	58.2	68	48	
316	137	377	106	18.1	15	83	53	58.2	80	48	
								58.6	86	58	Improved Same Much weaker, nauseated
								58.9	82	48	
316	137	376	106		21	76	52	58.6	78	60	
315	137	373	104	17.3	15	86	50	57.7	78	64	Improved by evening Much stronger Satisfactory
								59.5	88	58	
								59.9	84	66	
								59.2	78	58	Feels well
								59.0	82	64	
								58.6	84	50	

which reduced the intake of sodium chloride to not more than 15 Gm. On November 27 the patient felt well and that night slept well. On the following day, November 28, she was weaker, and on November 29 she was unable to walk to the scales to be weighed. Her sleep was somewhat disturbed by restlessness,

nevertheless, she continued to feel well, and nausea, hiccup, abdominal pain and other symptoms of impending crisis were absent. In addition, the pulse was strong, and all the food served was eaten. On December 2, the eighth day after the intake of sodium and chloride had been restricted, the patient fainted while being weighed. Restlessness was increasing, and there was some nausea. Despite this the patient's condition did not suggest the development of a definite crisis.

During this period of seven days in which the patient had been deprived of sodium chloride, the urinary excretion of sodium and chloride steadily fell, and by December 1 the output in the urine both of sodium and of chloride was not much in excess of the intake of these ions. In other words, the metabolic response to the restriction of sodium chloride was very nearly like that which is

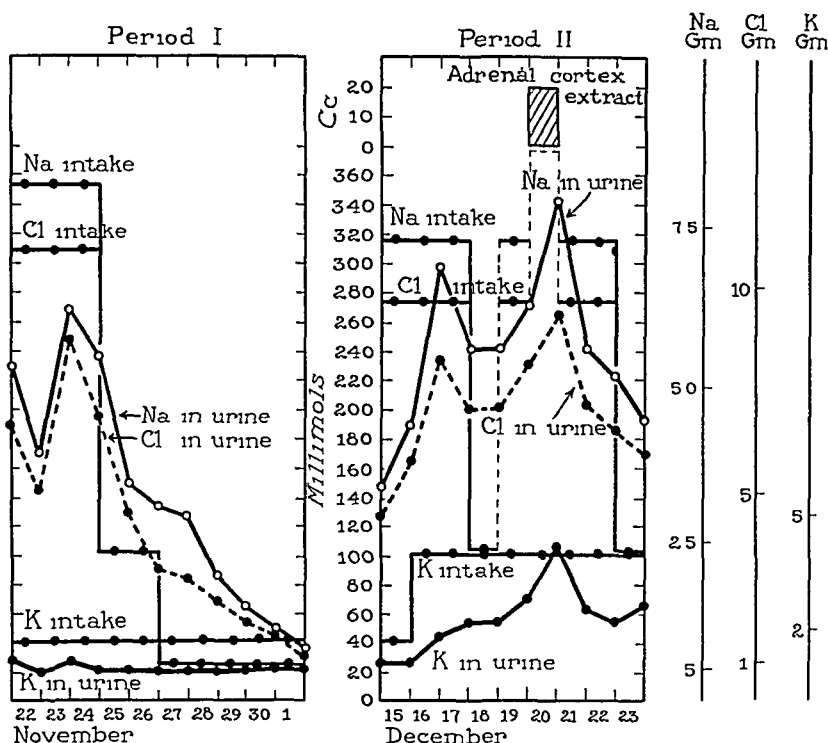


Chart 1 (case 1) —Metabolic studies of a patient with Addison's disease

observed in health, namely, the excretion was diminished sufficiently so that a loss of sodium and chloride was avoided. A slight depression of the levels of the ions of sodium and chloride in the blood plasma and an increase of the potassium ions to a high normal level were noted.

In the interval from December 2 to December 15 the patient was given extra sodium chloride and sodium citrate by mouth daily. In addition, 10 cc of extract of adrenal cortex¹⁶ was injected on December 7 and again on December 8, the purpose of this being to insure as adequate body stores of sodium and chloride as may have existed on November 25. During this interval the intake of potassium was held at the low level of approximately 16 Gm a day. The general condition of the patient became very satisfactory, certainly it was as good as before November 25. Beginning December 11 the sodium salts were administered by intravenous perfusions at twelve hour intervals so that changes could be made in the intake of salts without the patient's knowledge.

Observations from December 15 to 29 (metabolic data in table 1 and chart 1, period 2) From December 16 to 24, inclusive, 66 Gm of potassium citrate was added to the perfusing fluids. This amount represented 24 Gm of potassium and thus increased the daily intake of potassium from 16 to 4 Gm. The increased intake of potassium was followed immediately by a markedly increased excretion of both sodium and chloride. On December 18 the sodium salts were removed from the perfusing fluids, being replaced by dextrose, and the intake of sodium and chloride thus was reduced to the 6 Gm of sodium chloride contained in the food and its seasoning. The excretion of sodium chloride continued high and by the morning of December 19, just twenty-four hours after the withdrawal of the extra sodium salts, the patient was definitely worse, she had lost 3 pounds (1.3 Kg) and was very weak and sick.

On the evening of December 19 sodium chloride and sodium citrate were given by vein, and on December 20 the administration of sodium salts by mouth was resumed, also 20 cc of adrenal cortex extract was administered.

On December 21 the patient was much improved, and on December 22 she was still strong.

On December 23 the sodium salts again were withdrawn, the intake of potassium continuing unchanged, and the following morning, December 24, the patient again was seriously weak and nauseated. The deleterious effect of these relatively small doses of potassium citrate being greatly in evidence, the observations were brought to a close.

The patient was restored to a satisfactory condition by the intravenous injection of sodium chloride and sodium citrate. The intake of potassium was diminished to the previous level of 16 Gm a day, and after December 25 only 5 Gm of extra sodium chloride and 25 Gm of sodium citrate was given daily by mouth. On December 29 the patient was permitted to return to her home on this regimen.

In this case of Addison's disease of considerable severity the evidence indicates that a rigid restriction of sodium and chloride caused little disturbance of the metabolism of sodium and chloride and was reasonably well tolerated when the intake of potassium was low (16 Gm a day) but that the addition of only 24 Gm of potassium, as potassium citrate, provoked an increased excretion of sodium and chloride. Under these circumstances restriction of the intake of sodium and chloride precipitated symptoms of a crisis of Addison's disease. In the observation reported the addition of potassium citrate and the withdrawal of sodium salts were accomplished without the patient's knowledge, as all salts except the small amounts contained in the food were administered by intravenous perfusion. What appears in chart 1 to be a positive balance for sodium and chloride in period 2 of this experiment possibly is explained by the excretion of sodium and chloride in the feces. Analyses of the feces were not made.

CASE 2—Observations as to the Effect of the Level of Intake of Potassium on Addison's Disease, Also the Effect of Diuretic Drugs—The subject of this study was a woman 33 years old who, with the exception of diphtheria at the age of 3 years, a nervous breakdown at the age of 16 and rather frequent colds, was reasonably well until 1930. A severe infection of the upper respiratory tract,

called "flu," confined her to bed for a week in 1930, and from this she recovered very slowly. The body weight had been 148 pounds (67.1 Kg) before, but it fell gradually, and the patient also lost endurance. She first noticed pigmentation of the face in 1933, which gradually involved the entire body. In 1935 a dentist called her attention to discoloration of the margins of the gums. Early in 1935 frequent attacks of hiccup, much nausea and anorexia and greatly increased weakness developed. During a menstrual period in July there were severe pains in the lower part of the abdomen. A physician was called. A diagnosis of Addison's disease was made, and treatment was started with daily injections of a commercial extract of adrenal cortex¹⁵. For some time before this the patient had craved salt and had used salt in place of sugar.

The patient first came to the clinic on July 19, 1935. She then was as dusky as a Negress and was deeply pigmented on the palms and fingers of the hands, over the bridge of the nose, around the mouth and at the points of pressure. The gingival margins also were pigmented. She was very weak and weighed 107 pounds (48.5 Kg). The blood pressure was 114 mm of mercury systolic and 72 diastolic. The pulse rate was normal. Roentgenograms revealed no evidence of tuberculosis of the lungs and no calcification in the region of the adrenal glands. The value for hemoglobin was 10.9 Gm per hundred cubic centimeters. The flocculation test for syphilis was negative.

Under treatment with extract of adrenal cortex, sodium chloride and sodium citrate improvement was observed, and the patient soon said she felt as well as at any time after the onset of her illness. An attempt was made at this time to restrict the intake of sodium and chloride and to give only extract of adrenal cortex. This was only moderately successful, and when the administration of extract of adrenal cortex was discontinued, the sodium content of the blood serum fell from 313 to 282 mg per hundred cubic centimeters, the urea content rose from 30 to 40 mg and symptoms of crisis developed within forty-eight hours. The diet at that time probably contained about 4 Gm of potassium.

After restorative treatment had been given the patient left for her home with instructions to take extract of adrenal cortex daily as well as 10 Gm of extra sodium chloride and 1 level teaspoonful of sodium bicarbonate. At a visit to the office on September 26 she was stronger, her weight had increased to 115 pounds (52.1 Kg) and she was free from symptoms. Her blood pressure was 115 mm of mercury systolic and 70 diastolic. At another visit on November 8 she was feeling very well. Her blood pressure was 118 systolic and 72 diastolic. She had been able to work at household tasks.

On December 21 for no reason that was apparent at the time, symptoms of crisis developed suddenly: hiccup, nausea, vomiting, abdominal pain and great weakness. It is not improbable that the episode was precipitated by eating dates, figs, nuts and other "holiday foods" with a high content of potassium. More extract of adrenal cortex and more sodium chloride were given, but improvement was slow. The patient returned to the clinic on Jan 16, 1936, and was placed in the hospital on that date.

Observations from Jan 18 to Feb 1, 1936 (metabolic data in table 2 and chart 2, period 1). A study was made of the effect of restricting the intake of sodium and chloride with the intake of potassium at a low level. On January 18 the diet was adjusted so that its estimated content of potassium was 1.6 Gm. The total intake of sodium chloride was made to approximate 16 Gm a day, and sodium citrate was given in a daily dose of 5 Gm. The administration of extract of adrenal cortex was discontinued.

On January 20 the patient was comfortable, and the intake of sodium salts was reduced to the sodium chloride contained in the food and its seasoning (15 Gm in the food and 45 Gm used as seasoning). The patient became weaker, and on January 24 some hiccup, vomiting and abdominal pain occurred. On January 25 and 26 she was free from these symptoms but continued to be weak, and it was decided that the amount of salt required by the patient exceeded what she was receiving.¹⁷

During this period of seven days in which the intake of sodium chloride was restricted, the urinary excretion of sodium and chloride steadily diminished, and after the third day the output in the urine was less than the intake. On the other hand, the levels of sodium and chloride in the blood declined, and the urea content of the blood increased from 24 to 42 mg per hundred cubic centimeters. The patient lost 12 Kg in weight during the first three days but thereafter lost no more.

On January 27 the intakes of sodium and chloride were increased. Between January 30 and February 5 the condition of the patient was again entirely satisfactory.

Observations from February 6 to 14 (metabolic data in table 2 and chart 2, period 2). A study was made of the effect of increasing the intake of potassium. On February 6 the daily intake of potassium, which up to that time had remained at approximately 16 Gm, was increased to 4 Gm by the administration daily of capsules of 66 Gm of potassium citrate (24 Gm of potassium). The administration of extra sodium chloride and sodium citrate was not interrupted. Nausea developed on the afternoon of the first day of administration of the extra amount of potassium. The next day, February 7, the face was drawn, and the patient was hiccuping. That night she was restless and sleepless. On February 8 the weakness had increased, and by the morning of February 9, after another sleepless night, the patient was extremely weak, and the respirations were irregular. A crisis was impending. The patient's weight had fallen from 47.7 to 45.6 Kg in four days. The urinary excretion of sodium and chloride was markedly increased, the levels of sodium and chloride in the blood fell and a retention of potassium and urea was evident. The potassium content increased from 18.8 to 27.6 mg per hundred cubic centimeters.¹⁸

On February 9 restorative treatment was administered. It consisted of the intravenous injection of large amounts of sodium chloride, sodium citrate and extract of adrenal cortex, and by February 15 the patient again felt well and had regained her lost weight.

17 A later review of the record of this case gives the impression that the restriction of sodium and chloride between January 20 and 27 would have been tolerated better had the patient not been menstruating. Menstruation started on January 21 and continued until January 27. All the pain was pelvic. At no time did the clinical picture resemble that of an impending crisis. Thus the weakness never was such that the patient could not stand for her daily weighing. Her face did not look drawn, and the respirations never were of the hyperpneic type usually observed when a patient is in a serious condition.

18 This patient, receiving abundant sodium and chloride, reacted less stormily to the higher intake of potassium than the patients in cases 1 and 3, who had much smaller intakes of sodium and chloride. Unquestionably the high intakes of sodium and chloride protected her, but unquestionably the protection afforded was inadequate. The evidence is conclusive that potassium and potassium alone seriously aggravated her condition.

Observations from February 15 to 23 (metabolic data in table 2 and chart 2, period 3) A study was made of the effect of diuresis produced by the administration of ammonium nitrate and salyrgan. As considerable diuresis characteristically accompanies the development of symptoms of a crisis in patients with Addison's disease and since it accompanied the development of the critical con-

TABLE 2-

Date	Lot	Extract of Adrenal Cortex Amount, Cc	Intake								Twenty Four Hour Urine										
			Sodium Chloride, Gm	Sodium Citrate, Gm	Total Sodium		Total Chloride		Total Potassium		Total Nitrogen, Gm	Volume, Cc	Creatinine Nitrogen, Gm	Total Nitrogen, Gm	Sodium		Chloride		Potassium		
					Gm	Millimols	Gm	Millimols	Gm	Millimols					Gm	Millimols	Gm	Millimols			
																			U. in 100 G.		
Jan 1936																					
18			16	50	7.27	317	9.75	275	1.6	41	7.2	2,330	0.26	5.06	6.69	291	9.29	262	1.45	37	314
19			16	50	7.27	317	9.75	275	1.6	41	7.2	2,060	0.32	6.04	6.69	291	9.25	261	1.54	39	
20			6		2.37	103	3.65	103	1.6	41	7.2	1,900	0.31	6.66	6.53	284	8.63	234	1.33	34	317
21			6		2.37	103	3.65	103	1.6	41	7.2	2,460	0.27	5.87	5.08	221	7.18	202	1.44	37	
22			6		2.37	103	3.65	103	1.6	41	6.9	1,400	0.29	6.05	3.52	153	4.90	138	1.27	33	35
23			6		2.37	103	3.65	103	1.6	41	4.9	620	0.28	6.08	2.08	90	3.15	89	1.16	30	300
24			6		2.37	103	3.65	103	1.6	41	5.7	450	0.20	4.56	1.18	51	1.83	52	0.74	19	
25			6		2.37	103	3.65	103	1.6	41	6.2	535	0.25	5.75	1.49	65	1.13	32	0.95	24	
26			6		2.37	103	3.65	103	1.6	41	6.0	900	0.20	4.96	1.48	64	2.41	68	0.95	24	
27			11	2.5	4.83	210	6.72	189	1.6	41	5.2	1,300	0.29	7.05	2.48	108	3.75	106	1.53	39	35
28			11	2.5	4.83	210	6.72	189	1.6	41	6.8	860	0.23	5.76	2.55	111	3.46	98	1.44	38	
29			21	7.5	9.77	423	12.80	360	1.6	41	6.4	795	0.28	6.06	2.79	121	4.03	114	1.77	45	
30			16	5.0	7.27	317	9.75	275	1.6	41	6.8	1,010	0.24	5.53	2.75	120	3.81	107	1.24	32	35
31			16	5.0	7.27	317	9.75	275	1.6	41	7.2	1,100	0.25	4.70	3.01	131	3.83	108	1.19	30	
Feb 1			26	10.0	12.19	529	15.85	445	1.6	41	5.9	1,100	0.20	3.33	3.39	147	4.27	120	1.02	26	
Period 2—Effect of Increasing																					
2			16	5.0	7.27	317	9.75	275	1.6	41	5.5	1,100	0.27	2.99	3.32	144	4.57	129	0.97	25	
3			16	5.0	7.27	317	9.75	275	1.6	41		1,440	0.26	2.97	3.74	163	5.16	146	0.85	22	35
4			16	5.0	7.27	317	9.75	275	1.6	41	7.1	630	0.25	2.48	3.36	146	5.37	155	0.92	24	
5			16	5.0	7.27	317	9.75	275	1.6	41	7.1	740	0.26	2.57	3.64	158	4.54	128	0.93	24	310
6			16	5.0	7.27	317	9.75	275	4.0	103	5.4	1,060	0.26	2.34	4.00	174	5.43	153	1.15	29	
7			16	5.0	7.27	317	9.75	275	4.0	103	6.2	2,280	0.24	2.81	6.84	297	8.17	230	1.90	40	
8			16	5.0	7.27	317	9.75	275	4.0	103	7.2	1,690	0.24	2.61	6.82	297	8.10	228	2.44	62	310
9	72	20.0	36	15.0	17.10	745	18.70	535	1.6	41	6.7	1,210	0.21	2.24	4.75	207	5.74	162	2.23	57	304
10	72	10.0	26	10.0	12.19	529	15.85	445	1.6	41	6.2	1,660	0.28	3.52	4.76	207	7.30	206	4.56	107	
11			16	5.0	7.27	317	9.75	275	1.6	41	6.7	640	0.19	1.84	1.74	76	2.79	79	1.26	32	
12	77	5.0	16	5.0	7.27	317	9.75	275	1.6	41	7.1	800	0.26	1.99	2.11	92	3.32	94	1.13	29	
13	77	5.0	16	5.0	7.27	317	9.75	275	1.6	41	6.7	1,660	0.27	2.96	2.46	107	3.82	108	1.14	29	
14	81	5.0	16	5.0	7.27	317	9.75	275	1.6	41	6.9	1,760	0.28	2.60	3.07	134	4.10	116	0.84	22	
Period 3—Effect																					
15			16	5.0	7.27	317	9.75	275	1.6	41	6.5	1,760	0.27	2.59	4.19	182	5.61	158	0.94	24	371
16			16	5.0	7.27	317	9.75	275	1.6	41	7.2	1,900	0.26	2.83	4.68	204	6.24	176	1.10	28	
17		3.0*	16	5.0	7.27	317	9.75	275	1.6	41	6.4	2,285	0.27	3.24	4.66	203	6.32	178	1.16	30	
18		4.5*	16	5.0	7.27	317	9.75	275	1.6	41	6.1	1,800	0.27	3.31	4.09	178	5.58	157	1.16	30	372
19			16	5.0	7.27	317	9.75	275	1.6	41	7.2	1,900	0.26	3.59	4.43	192	6.01	170	1.14	37	
20		1.0†	16	5.0	7.27	317	9.75	275	1.6	41	7.0	1,630	0.26	3.01	3.00	130	4.40	124	1.09	28	
21			16	5.0	7.27	317	9.75	275	1.6	41		1,830	0.28	3.15	3.57	155	5.35	157	0.91	23	
22			16	5.0	7.27	317	9.75	275	1.6	41		1,770	0.25	2.80	3.35	146	4.70	133	1.15	29	

* Ammonium nitrate, grams

† Salyrgan, cubic centimeter

dition in this case when potassium was administered and because such a loss of water alone might account for the loss of chloride and consequently for the symptoms, control observations were made in this third period after the administration on February 16, 17 and 18, respectively, of diuretic doses of ammonium nitrate. This salt provoked an increased volume of urine and the loss of 14 Kg

of weight Some nausea occurred, and on February 17 the breakfast was vomited, also, there was some increase in weakness but not enough to interfere with the patient's being up and about On the morning of February 19 she said she felt very well A loss of sodium chloride did not accompany the diuresis provoked by this administration of ammonium nitrate, and the concentrations of the electro-

Data in Case 2

Blood Plasma								Blood Pressure, Mm of Mercury		Clinical Observations	
Sodium	Chloride		Potassium		Urea, Mg per 100 Cc	Sugar, Mg per 100 Cc	Carbon Dioxide, Vol %	Body Weight, Kg	Systolic		Diastolic
Millimols per Liter	Mg per 100 Cc	Millimols per Liter	Mg per 100 Cc	Millimols per Liter							
Chloride, with Intake of Potassium at Low Level											
137	373	105	18.0	4.6				48.5	105	55	Began diet low in potassium
								48.5	110	50	
136	366	103	19.1	4.9	24	85	46.2	48.5	105	45	
								47.7	100	45	Weakness, menstruation began
134	351	99	21.4	5.5	24	94	46.1	47.3	105	50	Weaker, sleepless
130	346	98	19.7	5.0	30	98	50.0	47.5	110	40	Same
								47.5	100	60	Vomiting and hiccup
								47.7	100	60	Very weak
								47.3	96	56	Same, still menstruating
124	317	89	21.3	5.5	42	95	47.5	47.0	96	50	Weaker
								48.0	80	50	Improved, menses stopped
								47.0	85	60	Stronger
125	327	92	20.1	5.1				46.7	80	60	No change
								47.5	94	42	Stronger
								47.7	98	56	No change
Intake of Potassium											
								48.4	94	44	No change
138	361	102	17.5	4.5	18	80	52.8	47.7	96	40	Doing well
								47.7	92	44	No change
137	367	104	18.8	4.8	20	89	57.6	48.0	92	54	Looks and feels well
								47.7	94	56	Walking more than usual
								46.7	86	52	Weaker, haggard, hiccup
135	356	100	23.0	5.9		102		46.4	86	52	Great weakness, anorexia
132	356	100	27.6	7.1	27			45.6	84	50	Restorative treatment given
								46.6	80	50	Much improved, slept well
								47.0	85	45	Walked 6 blocks
								47.7	80	62	
								18.2	78	58	Appetite good
								47.7	104	70	Doing well
of Diuretics											
140	374	106	17.2	4.4	14	86	53.8	47.7	92	54	No change
								47.7	96	58	
								47.3	90	52	Feels well, looks well
140	368	104	19.4	5.0	14	82	52.9	47.0	84	50	Weaker, some nausea
								46.7	92	60	Tired, but up and about
								46.3	94	60	Weak, but up and about
								47.3	92	58	Feels well but tired
								47.7	94	60	Feels very well

lytes of the blood were not altered On February 20 1 cc of salyrgan was administered intravenously This also produced no ill effects

On February 21 and 22 the patient felt very well, and on February 23 she was dismissed, with instructions to continue on the diet low in potassium and to take 10 Gm of "extra" sodium chloride and 5 Gm of sodium citrate daily

In this case of Addison's disease of great severity a restriction of the intake of potassium to approximately 16 Gm a day permitted limiting the sodium and chloride to the salt in the food and that used for its seasoning (6 Gm) for a period of six days. In period 2 increasing the intake of potassium from 16 to 4 Gm a day, by giving potassium as potassium citrate in capsules, precipitated a markedly increased urinary excretion of sodium and chloride and the rapid development of symptoms of a crisis of Addison's disease. This occurred despite the administration of extra sodium chloride and sodium citrate.

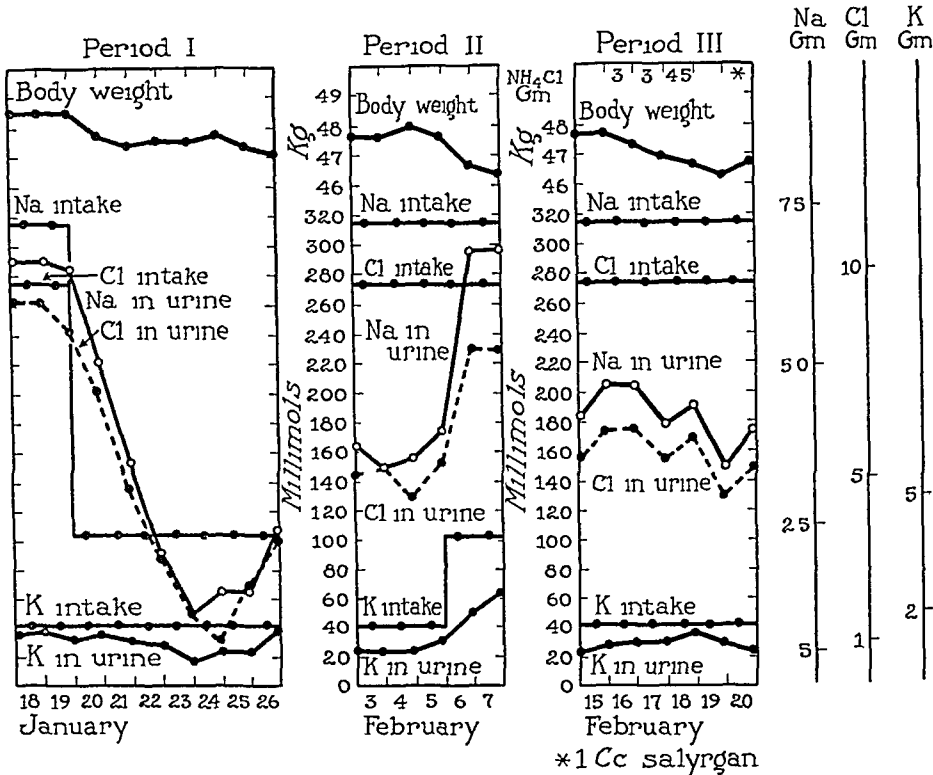


Chart 2 (case 2) —Metabolic studies of a patient with Addison's disease

In period 3 the diuresis produced by the administration of ammonium nitrate was not accompanied with a loss of sodium and chloride or with the development of serious symptoms

CASE 3—*Observation on the Effect of the Level of Intake of Potassium in Addison's Disease*—The subject of this study was a woman aged 37 who in 1913 had had an operation for acute tuberculous salpingitis and peritonitis. Signs and symptoms referable to Addison's disease developed in the autumn of 1933, consisting of fatigue, anorexia, loss of weight, a few black freckles and slight pigmentation of the gums.

When the patient was examined at the clinic in February 1934, Addison's disease was suspected, despite the absence of diffuse bronzing of the skin. Eight grams of "extra" sodium chloride was prescribed in the form of pills. This treat-

ment was reasonably effective, and at the time of a second visit, in September 1934, the condition of the patient was at least no worse than it had been

The patient was placed in the hospital in September 1934. In order to settle any doubts about the diagnosis of Addison's disease, the salt pills were withheld, and the diet was made salt poor. Nausea and hiccup developed almost at once, and within two days the patient was in a state of collapse, with severe abdominal pain and cyanosis. Injecting sodium chloride and extract of adrenal cortex restored her, and she was then treated with extract of adrenal cortex without extra salt, the salt in the food amounting to approximately 6 Gm. The patient stood this for about three days, when she collapsed, so that restorative doses of sodium chloride again were needed. Later, while receiving treatment with extract of the anterior lobe of the pituitary gland, she tolerated restriction of sodium chloride for eight days,¹⁹ as has been described before.²⁰

The patient returned to her home, under continuous treatment with extract of adrenal cortex and extra sodium chloride, and remained well until about February 1. She was then brought to the hospital in impending crisis, which had developed following an attack of infection of the upper respiratory tract. Restorative treatment was administered, and the patient remained well until the period of observation reported here. She entered the hospital at our request on October 6. She had been receiving daily 3 cc of extract of adrenal cortex by subcutaneous injection and 10 Gm of sodium chloride and 1 level teaspoonful of sodium bicarbonate by mouth. Examination revealed no abnormality not previously noted, except some pigmentation of the skin of the knees and wrists and of the creases of the palms. Roentgenograms of the region of the adrenal glands did not reveal calcification.

Observations from October 6 to November 3 (metabolic data in table 3 and charts 3 and 4, period 1). A study was made of the effect of restriction of the intake of sodium and chloride with the intake of potassium at a low level. On October 6 the diet was made to contain approximately 1.6 Gm of potassium and 6 Gm of sodium chloride. In addition between October 6 and 15, 10 Gm of sodium chloride and 5 Gm of sodium citrate were given by mouth. The dose of extract of adrenal cortex was continued as before at 3 cc a day.

On October 7 the sodium chloride in the blood serum measured 676 mg per hundred cubic centimeters, the sugar 78 mg and the urea 30 mg.

On October 16 the administration of "extra" sodium chloride and sodium citrate was discontinued, and the sodium chloride in the food was restricted to a maximum of not more than 1.5 Gm a day. At the same time the dose of extract of adrenal gland was increased to 15 and later to 25 cc a day. Menstruation commenced on October 18, and with it there was some cramping in the lower part of the abdomen, together with weakness and vertigo. Otherwise there were no untoward symptoms. On October 20, although menstruation was continuing, the unpleasant abdominal cramps had disappeared, and the patient looked and felt very well. She walked two miles. Her appetite was good. A week later, on October 27 she was still in good condition. Twelve days without trouble had

19 This experiment needs repeating in the light of our present knowledge of the importance of controlling the potassium content of the diet.

20 Wilder, R. M. The Use of Anterior Lobe Pituitary Extract in the Treatment of Addison's Disease, *Proc Staff Meet, Mayo Clin* 9:689-693 (Nov 14) 1934.

then passed since the intake of sodium and chloride had been so rigidly restricted. During that time the sodium and chloride contents of the urine had decreased, as they would under similar conditions in the urine of a person in good health who had been deprived of sodium and chloride, thus the body stores of these elements were but little affected.

TABLE 3

Date	Lot	Extract of Adrenal Cortex Amount, Cc	Intake								Twenty Four Hour Urine									
			Sodium Chloride, Gm	Sodium Citrate, Gm	Total Sodium		Total Chloride		Total Potassium		Total Nitrogen, Gm	Volume, Cc	Creatinine Nitrogen, Gm	Total Nitrogen, Gm	Creatine Nitrogen, Mg	Sodium		Chloride		Potassium
					Gm	Millimols	Gm	Millimols	Gm	Millimols						Gm	Millimols	Gm	Millimols	Gm
Oct 1935																				
13	47	3	16.0	5	7.27	317	9.75	275	1.6	41	7.0	1,080	0.26	5.03		4.18	181	5.21	147	0.95
14	47	3	16.0	5	7.27	317	9.75	275	1.6	41	6.6	1,570	0.30	5.34		5.94	258	6.77	191	1.08
15	52	15	16.0	5	7.27	317	9.75	275	1.6	41	6.4	1,430	0.29	5.37		5.95	258	7.79	220	1.25
Period 1—Effect of Restricting Intake of Sodium																				
16	52	15	1.5		0.59	26	0.91	26	1.6	41	6.2	1,940	0.29	4.95		5.35	232	7.43	210	1.52
17	52	15	1.5		0.59	26	0.91	26	1.6	41	6.6	2,650	0.28	4.68		4.11	178	5.88	166	1.00
18	52	25	1.5		0.59	26	0.91	26	1.6	41	6.4	2,180	0.28	4.55		2.93	127	4.09	115	0.81
19	32	25	1.5		0.59	26	0.91	26	1.6	41	6.2	1,360	0.25	3.34		2.01	88	2.73	77	1.01
20	52	20	1.5		0.59	26	0.91	26	1.6	41	7.0	1,290	0.30	4.99		1.43	62	1.65	47	0.81
21	52	20	1.5		0.59	26	0.91	26	1.6	41	6.4	1,520	0.27	4.89		0.97	42	1.35	38	0.79
22	52	10	1.5		0.59	26	0.91	26	1.6	41	6.4	1,480	0.28	5.60		1.03	45	1.32	37	0.72
23	52	10	1.5		0.59	26	0.91	26	1.6	41	6.4	1,870	0.27	5.14		1.20	52	1.33	37	0.65
24	52	10	1.5		0.59	26	0.91	26	1.6	41	6.4	1,710	0.27	4.81		1.36	59	1.69	48	0.73
25	52	10	1.5		0.59	26	0.91	26	1.6	41	6.4	1,495	0.26	4.23		1.13	49	1.55	44	0.81
26	52	10	1.5		0.59	26	0.91	26	1.6	41	6.4	1,610	0.25	3.94		1.15	50	1.29	36	0.53
27	32	10	1.5		0.59	26	0.91	26	1.6	41	6.4	1,680	0.30	4.70		1.19	52	1.78	50	1.23
28			1.5		0.59	26	0.91	26	1.6	41	6.4	1,410	0.29	4.66		1.00	44	1.26	35	0.99
29			1.5		0.59	26	0.91	26	1.6	41	6.4	1,790	0.25	4.38		1.49	65	1.43	40	0.69
30			1.5		0.59	26	0.91	26	1.6	41	6.4	1,720	0.26	4.91		2.02	88	2.23	63	1.16
31			1.5		0.59	26	0.91	26	1.6	41	6.4	2,040	0.28	5.24		2.02	88	2.28	64	1.16
Nov																				
1			1.5		0.59	26	0.91	26	1.6	41	6.4	2,040	0.20	4.62		1.66	72	2.03	57	0.99
2			1.5		0.59	26	0.91	26	1.6	41	6.4	1,875	0.16	3.51		1.25	54	1.52	43	0.87
3			16.0	5	7.27	317	9.75	275	2.0	51	6.4	1,045	0.26	3.98		2.58	113	3.97	112	2.13
Period 2—Effect of Incr																				
Jan 1936																				
5			16.0	5	7.27	317	9.75	275	1.6	41	6.4									
6			16.0	5	7.27	317	9.75	275	1.6	41	6.4									
7			16.0	5	7.27	317	9.75	275	1.6	41	6.4									
8			16.0	5	7.27	317	9.75	275	5.8	148	12.8	1,050	0.25	4.86	6	5.13	223	7.96	224	1.36
9			15.2	5	6.97	302	9.26	260	5.8	148	12.0	2,120	0.29	5.83		7.32	317	10.78	304	2.53
10			15.2	5	6.97	302	9.26	260	5.8	148	12.0	1,595	0.28	6.86		9.73	423	14.61	412	3.14
11	52	3	16.5	5	7.48	326	10.10	284	5.5	141	12.8	1,445	0.27	6.74		8.60	374	13.66	385	3.52
12	52	10	16.5	5	7.48	326	10.10	284	5.5	141	11.7	2,116	0.31	9.99	99	9.27	404	13.82	390	4.14
13	52	20	1.5		0.59	26	0.91	26	5.5	141	10.9	1,775	0.29	9.76	81	7.93	345	10.74	304	3.80
14	52	20	35.0	5	14.77	642	21.40	600	1.6	41	6.6	1,760	0.20	7.89		4.08	178	6.47	182	3.29
15	71	10	16.0	5	7.27	317	9.75	275	1.6	41	4.8									
16			16.0	5	7.27	317	9.75	275	1.6	41	5.1									

* The specimen of urine reported on represents that passed from 7 a m to 7 p m on January 13, a twelve hour period. The addition at 7 p m, and 20 cc more of extract of adrenal cortex was given after 7 p m, with 800 cc of a solution containing 16 Gm.

On October 28 the administration of extract of adrenal cortex was discontinued. On October 29 and 30 there were no symptoms. The patient's sleep during the night of October 30 and 31 was broken between 12 and 2 a m by restlessness. On October 31 weakness was increasing, and the appetite was lost. That night sleep was again broken by restlessness. Until then the patient had been up and about and had even been outdoors for short walks. On November

20 Gm a day, and she was allowed 10 Gm of sodium chloride and 5 Gm of sodium citrate a day by mouth. She felt well and was able to do her housework. She returned to the hospital at our request on Jan 5, 1936.

Observations from Jan 5 to 17, 1936 (metabolic data in table 3 and charts 3 to 5, period 2). A study was made of the effect of increasing the intake of potassium in the food. From January 5 to 7, inclusive, the diet was adjusted so that the intake of potassium did not exceed 16 Gm a day. Extra sodium chloride and sodium citrate were administered by mouth. This regimen approximated that to which the patient had been adhering for the preceding two months.

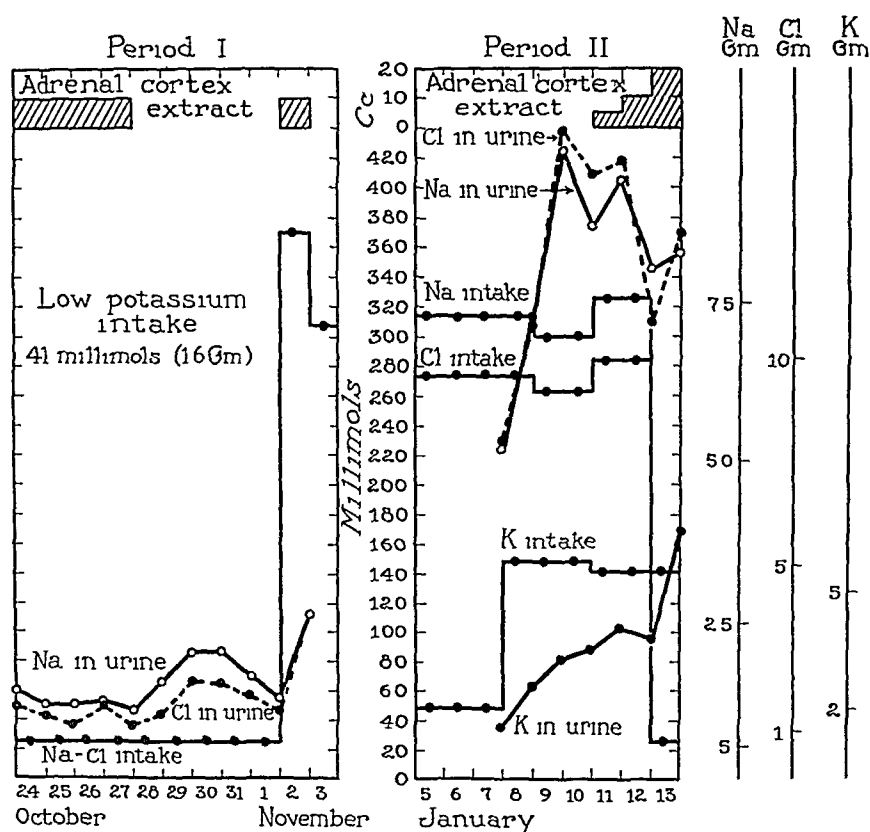


Chart 3 (case 3) —Metabolic studies of a patient with Addison's disease

On January 8 the level of the intake of potassium was increased to 58 Gm a day. This was accomplished by the inclusion in the diet of foods rich in potassium. Within twenty-four hours significant disturbances were observed in the urinary excretion of sodium and chloride and in the level of the sodium and chloride in the blood. The excretion of sodium and chloride increased. Diarrhea occurred on January 10 and 11. It was arrested by a dose of bismuth subnitrate and by arranging the diet so that it contained less laxative foods. This reduced the intake of potassium to 55 Gm a day. It was suggested that the high intake of potassium was responsible for the diarrhea, the symptom having been observed occasionally in adrenalectomized dogs. Extract of adrenal cortex was given in small doses beginning on January 11.

On January 11, although the diarrhea had stopped, the patient was weak. On January 12 she felt as sick as she had at any time in the period from Oct 16

to Nov 3, 1935, although on Jan 11 and 12, 1936, she was receiving sodium salts in large doses and extract of adrenal cortex in a small dose, and from Oct 15 to Nov 3, 1935, the intake of sodium and chloride were restricted to a minimum, and after October 27 she received no extract of adrenal cortex. She complained on January 13 of a great loss of strength, of deafness and of epigastric distress. She was apprehensive and depressed. On January 13 the "extra" sodium chloride and sodium citrate were withheld, the total intake of sodium and chloride being reduced to that contained in the food. Anorexia prevented the patient from eating much of the food. At 1 10 p m, after the noon meal, an episode of hiccupping occurred which lasted for ten minutes. At 3 p m the patient tried to walk but could not stand. At 7 30 p m she was very weak and was failing.

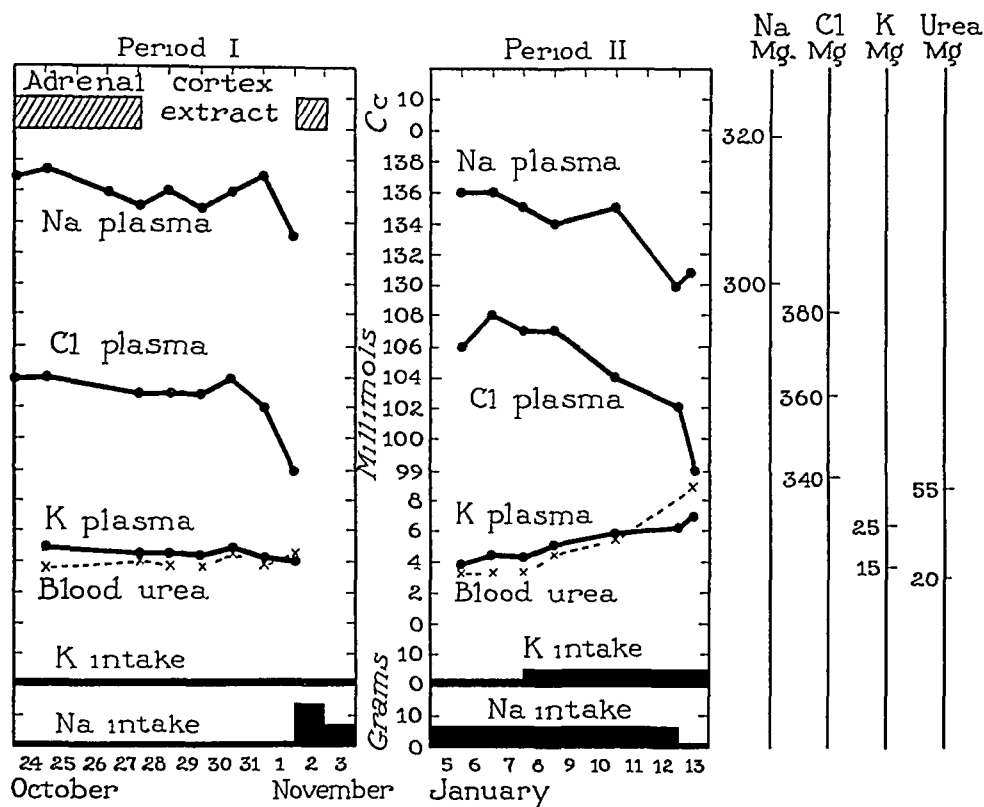


Chart 4 (case 3) —Further metabolic studies of a patient with Addison's disease

rapidly. The respirations were hyperpneic, the radial pulse was palpated with difficulty and the patient looked haggard. Between 7 a m and 7 p m she had passed nearly 2,000 cc of urine, and her body weight had declined 2 pounds (0.9 Kg), it being 4 pounds (1.8 Kg) less than on January 9. A crisis obviously impended, and restorative treatment therefore was necessary that evening. A solution containing 16 Gm of dextrose, 16 Gm of sodium chloride, 4 Gm of sodium citrate and 20 cc of extract of adrenal cortex was administered.

On January 14 the patient felt well until in the afternoon, when again she had some symptoms of adrenal insufficiency. Another intravenous injection was given. Her condition then was good, and by January 17 the lost weight had been regained and she could be permitted to return to her home.

In this case of Addison's disease of moderate severity the evidence is conclusive of intolerance to potassium and benefit by limiting the

intake of it. In the period elapsing from Jan 5 to 14, 1936, when the food provided from 5.5 to 5.8 Gm of potassium, large losses of sodium, chloride and nitrogen occurred, together with marked creatinuria (charts 3 to 5). This occurred despite a large intake of sodium and chloride and the administration of small doses of extract of adrenal cortex. In an earlier period, from Oct 27 to Nov 6, 1935, when the diet was so constructed that the daily intake of potassium did not exceed 1.6 Gm, the patient tolerated an almost complete deprivation of sodium and chloride for a period of seventeen days. Extract of adrenal cortex was administered during the first twelve days of this period but not during the last five.

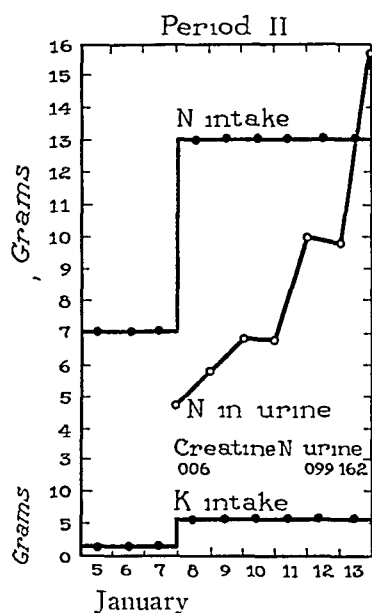


Chart 5 (case 3) — Further metabolic studies, period 2

Of significance also is the fact that with a diet low in potassium and only moderate doses of extra sodium and chloride, the patient remained in good health at home for sixty-six days without the benefit of injections of extract of adrenal cortex, which previously, when attention was not directed to the potassium content of the diet, had been necessary.

The ill effect of the larger intake of potassium from Jan 8 to 13, 1936, inclusive, is not attributable to diuresis. The amount of water excreted daily was not more than that excreted between Oct 16 and Nov 3, 1935, when the intake of potassium was lower. The correlation is with the urinary excretion of sodium and chloride—in the periods when the intake of potassium was low the excretion did not greatly exceed the intake of sodium and chloride, in the period when the intake of potassium was high it did.

COMMENT

That potassium is toxic when perfused through the isolated heart or other muscles or when injected in sufficient amounts into an intact animal is a matter of common knowledge. Also that the kidney of a patient with adrenal insufficiency is relatively less competent than normal has been known since its demonstration in 1916 by Marshall and Davis²¹. Hastings and Compere²² in 1931 showed that the concentration of potassium in the blood of dogs increases after the removal of the adrenal glands. The concentration before death reached 20 millimols per liter, a value which was found to be comparable to the concentration of potassium in the blood of normal dogs killed by the injection of a large amount of potassium. Their statement that this observation "might be of importance in reaching an understanding of the cause of death following the functional or surgical removal of the suprarenal glands" proves to have been prophetic.

Concentrations of plasma potassium as great as those recorded by Hastings and Compere have not been encountered among patients with Addison's disease, but that retention of potassium may occur in Addison's disease has been shown by Loeb and others²³. In twenty-four cases Marañón and Collazo²⁴ used Kramer's method of analysis and obtained values ranging from 21.7 to 49.5 mg per hundred cubic centimeters (5.5 to 12.7 millimols per liter). The normal concentration of potassium in the plasma is from 16 to 20 mg per hundred cubic centimeters (4 to 5 millimols per liter). The Spanish investigators attributed the dehydration of Addison's disease to a disturbance of equilibrium between the potassium and the sodium of the plasma and made the suggestion that one of the physiologic activities of the hormone of the adrenal cortex is the maintenance of this regulation. This equilibrium is not easily disturbed. If one adrenal gland remains intact, as was shown by Loeb, Atchley, Benedict, and Leland,¹ large doses of potassium salts may be given without harm. In one experiment from 5 to 7 Gm of potassium chloride was administered daily to a dog deprived of one adrenal gland, with the purpose of inducing an increased excretion of sodium. No loss of sodium occurred, and the proportions of potassium and sodium in the plasma remained unchanged.

21 Marshall, E. K., Jr., and Davis, D. M. The Influence of the Adrenals on the Kidneys, *J. Pharmacol. & Exper. Therap.* **8** 525-550 (Sept.) 1916.

22 Hastings, A. B., and Compere, E. L. Effect of Bilateral Suprarenalec-tomy on Certain Constituents of the Blood of Dogs, *Proc. Soc. Exper. Biol. & Med.* **28** 376-378 (Jan.) 1931.

23 Loeb, R. F. Chemical Changes in the Blood in Addison's Disease, *Science* **76** 420-421 (Nov. 4) 1932.

24 Marañón, G., and Collazo, J. A. Die Deshydrirung in der Addisonschen Krankheit und ihr Mechanismus, *Wien. Arch. f. inn. Med.* **27** 189-200, 1935.

Urechia and his collaborators²⁵ suggested that the toxicity of the potassium ion and its action on muscle fiber explain the asthenia of Addison's disease, and Nicholson and Soffer²⁶ obtained a striking correlation between the concentration of potassium in the plasma of adrenalectomized dogs and the auricular fibrillation not infrequently encountered after adrenalectomy. The value for potassium in the animals in which fibrillations developed was never less than 52 mg per hundred cubic centimeters (13.3 millimols per liter), and in one animal it reached 92.5 mg per hundred cubic centimeters (23.6 millimols per liter). Auricular fibrillation has not been recorded in Addison's disease, but probably it has been looked for infrequently in the terminal stages, when the retention of potassium is at its maximum.

Harrop and his associates²⁷ (1933) also considered the extreme muscular weakness of adrenalectomized dogs to be due in part to the disturbance in the relative concentration of the basic ions in the tissue and body fluids and observed further that adrenalectomized dogs maintained with an extract of adrenal cortex and fed exclusively on meat (a food rich in potassium) were unusually sensitive to withdrawal of the extract. Harrop and his co-workers have also pointed out that the consequence of the loss of sodium chloride and water through the kidneys of adrenalectomized dogs recalled the studies of Gamble and his associates on dogs which had lost sodium chloride and water by drainage of pancreatic juice from a Pavlov fistula. "The greater rapidity of the appearance of serious symptoms on a meat diet without added salt, in which the fixed base is in large part potassium, and hence unsuited to the repair of plasma and the interstitial fluid loss was striking and also in keeping with the effects in suprarenalectomized dogs deprived of extract." Gamble and McIver in one of their papers commented on an earlier observation of Pavlov that a milk diet will considerably prolong the survival period of dogs suffering from a deficit of sodium resulting from a pancreatic fistula.

25 Urechia, C. I., Benetato, G., and Retezeanu. Le potassium sanguin apres extirpation des glandes surrénales, *Compt rend Soc de biol* **119** 439-440 (March 21) 1935.

26 Nicholson, W. M., and Soffer, L. J. Cardiac Arrhythmia in Experimental Suprarenal Insufficiency in Dogs, *Bull Johns Hopkins Hosp* **56** 236-243 (April) 1935.

27 Harrop, G. A., Weinstein, Albert, Soffer, L. J., and Trescher, J. H. The Diagnosis and Treatment of Addison's Disease, *J. A. M. A* **100** 1850-1855 (June 10) 1933. Harrop, G. A., Saffer, L. J., Ellsworth, Read, and Trescher, J. H. Studies on the Suprarenal Cortex. III. Plasma Electrolytes and Electrolyte Excretion During Suprarenal Insufficiency in the Dog, *J. Exper Med* **58** 36 (July) 1933.

Our idea that limiting the intake of potassium might favorably influence the course of Addison's disease thus was a rational deduction from indirect evidence already available

We are fully aware that the data of the present report are not as complete as might be desired. Analyses of the feces should have been made. More determinations of the excretion of creatine would have been helpful, and longer periods between changes of regimen would have been advantageous. It happened that the facilities of the laboratory at the time did not permit more extensive analytic determinations, and the necessary consideration of the welfare of the patients frequently interfered with the extension of the periods of observation. The data,

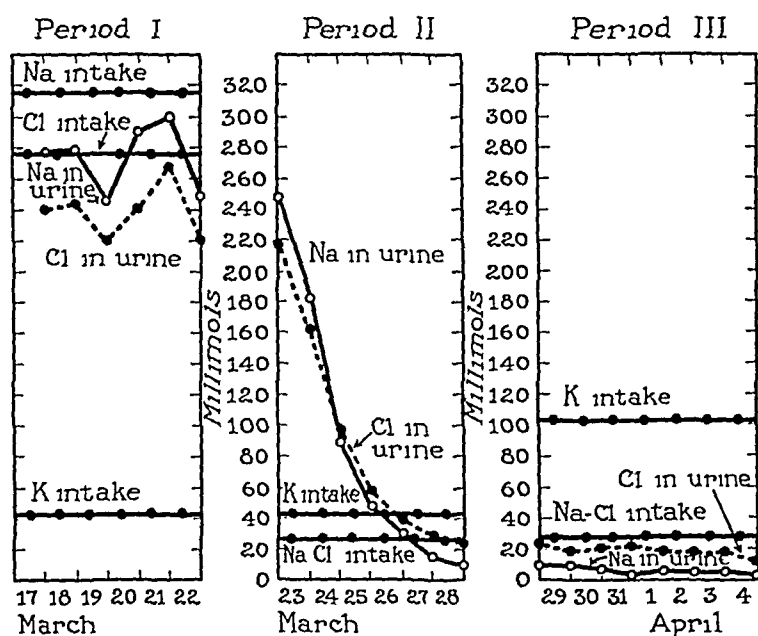


Chart 6—Metabolic studies of a normal subject

however, are sufficiently complete to reveal that low levels of intake of potassium are advantageous in Addison's disease, and this was the primary question for which we sought an answer. An intake of potassium not greater than that provided by a general diet (about 4 Gm) caused a loss of ions of sodium and chloride and the development of symptoms of crisis even when "extra" sodium chloride and sodium citrate were administered. A diet still higher in its content of potassium (period 2 in case 3) was correspondingly more disturbing and produced serious consequences which were not prevented even by treatment with "extra" sodium chloride, sodium citrate and small doses of extract of adrenal cortex. On the other hand, diets restricted in the content of potassium to approximately 1.6 Gm permitted the maintenance of all three patients without resort to injections of extract of adrenal cortex,

and under such circumstances even a rigid restriction of the intake of sodium salts was tolerable (cases 1 and 3) for a period of many days

That potassium in the maximal amounts received by these patients produces no untoward effects in normal subjects is perfectly obvious. The amounts involved are no greater than most persons receive each day with their usual meals. A series of observations on a normal subject comparable to those made with the patient in case 2 will be reported soon by two of us (Drs. Keplei and Adams) with Dr. Blum. The data of three periods of their study are shown in chart 6. It is clearly evident from them that increasing the intake of potassium from a low to a high level provoked no loss of sodium and chloride ions even when the intake of sodium and chloride was at a minimum. The feces were analyzed in their study, and since the observations were made in the winter, when the loss of sodium and chloride through the skin is at a minimum, the metabolic balances for sodium and chloride were perfectly reliable.

We have limited the evidence for reporting here to that obtained in only three cases of Addison's disease, because in these cases the metabolic data available were reasonably complete, our conclusions, however, are supported by additional experience. Recently a patient was placed in the hospital for withdrawal of salt from the diet, a procedure which Hannon and his associates proposed as a diagnostic test for adrenal insufficiency. It consists of restricting the intake of sodium and chloride to the salts of the unseasoned foods and has been supposed not to be tolerable for longer than a few days (five at the most) in any case of Addison's disease. The patient in question was not grossly pigmented, and her only symptom was weakness. She withstood the procedure for six days, no symptoms other than the original weakness developed and there were no greater changes for the values of sodium and chloride of the plasma than would be normal. At a later time, with a diet made to contain approximately 5.5 Gm. of potassium, the test was repeated. It was badly tolerated, and clear symptoms of adrenal insufficiency developed within three days. It now is apparent that attention must be paid to the potassium content of the diet in evaluating the results of this diagnostic procedure and likewise that all earlier experimental work on adrenal insufficiency, as well as procedures for the biologic assaying of extracts of adrenal cortex, will require revision from the standpoint of rigid control of the intake of potassium.

Two patients with obvious Addison's disease recently were admitted to the hospital in conditions bordering on crisis. In both cases the urea content of the blood and the potassium content of the plasma were elevated, whereas the sodium and chloride contents of the plasma were moderately depressed. In these cases, without resorting to injections of

extract of adienal cortex but by restricting the intake of potassium and adequately supplying calories, sodium chloride and sodium citrate, the patients were restored

It must be emphasized that subjects who are eating little or nothing because of nausea, are subsisting, in fact, on a metabolic mixture of food material high in potassium. This is because the endogenous supply of nutrients, on which they are depending, contains a large amount of tissue protein, which, like meat, is rich in potassium. Wastage of protein is characteristic of the crisis of Addison's disease, as is evidenced by negative nitrogen balances, and it is not improbable that the well known advantage of injections of dextrose in the treatment of the crises of Addison's disease depends, in part at least, on the "sparing effect" on protein of the calories supplied by the dextrose.

Diets Low in Potassium—The preparation of a palatable diet which will contain not more than 16 Gm of potassium requires the same careful planning as does that of a diet for a diabetic patient. Sherman's table showing the ash constituents of foods in percentage of the edible portion was compiled from various sources, and, while we have followed it to date in planning these diets, we are far from satisfied with it. A recent study by Davidson and LeClerc²⁸ indicated that there is a considerable variation in the content of potassium and other bases of vegetables obtained from different regions and that the mineral composition of vegetables seems to be correlated with the fertilizer treatment of the soil or the chemical composition of the irrigation water. Possibly also the meat of animals grazing on fields fertilized with potassium will be richer in potassium than the meat of other animals. These matters are being investigated by Sister Mary Victor and Miss Lydia Nelson, graduate students in nutrition of the Mayo Foundation. A practical suggestion already has come from the study being made by Sister Mary Victor—by boiling vegetables in two or three changes of water from 75 to 80 per cent or more of their salts, including potassium, can be removed. Potatoes, for instance, which normally contain more than 400 mg of potassium in each hundred grams, can be washed by this means and subsequently seasoned by the addition of table salt. Foods especially rich in potassium, containing, for example, more than 300 mg of potassium in each hundred grams, include the following: meats, fowl, fish of all kinds, potatoes, sweet potatoes, peas, beans, beets, cabbage, celery, chard, chestnuts, spinach and other greens, pumpkin, squash, parsnips, dried fruits (especially dates), figs, prunes, banana, pineapple,

28 Davidson, J, and LeClerc, J. A. The Variation in the Mineral Content of Vegetables, *J. Nutrition* 2: 55-66 (Jan.) 1936

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28 Davidson, J., and LeClerc, J. A. The Variation in the Mineral Content of Vegetables, *J. Nutrition* **2**: 55-66 (Jan.) 1936

nuts of all kinds, wheat, bran and molasses Obviously such foods must be used in moderation if the total intake of potassium is to be held below 1.6 Gm

The diet planned by Sister Mary Victor for the experiments here reported was as follows

LOW POTASSIUM DIET

Potassium, 1.6 Gm , Protein, 57 Gm , Calories, 2,350

Breakfast

Food	Grams	Approximate Measure
Orange juice	100	$\frac{1}{2}$ glass
Cornflakes	15	1 serving
Egg	50	One
Bread	50	2 slices
Butter	20	2 squares
Cream, 40 per cent fat	75	$\frac{3}{8}$ cup
Coffee if desired		

Dinner

Beef tenderloin (weight uncooked)	70	1 average serving
Potato, thrice boiled	100	1 average serving
Carrots	25	1 small serving
Celery	25	2 celery hearts
Grapefruit	55	4 sections
Bread	50	2 slices
Butter	25	$2\frac{1}{2}$ squares
Cream, 40 per cent fat	20	1 tablespoon
Tea or coffee if desired		

Supper

Cheese	40	2 cubic inches
Rice (weight dry)	25	1 average serving
Tomato	50	$\frac{1}{2}$ average serving
French dressing	15	1 tablespoon
Apple	80	$\frac{3}{4}$ average size
Bread	50	2 slices
Butter	25	$2\frac{1}{2}$ squares
Cream, 40 per cent fat	20	1 tablespoon
Tea or coffee if desired		

This diet, and indeed all the diets low in potassium that we have been able to plan, contain what seems to be an adequate amount of protein but a bare minimum of calcium and other minerals The content of vitamins A and C is adequate, but the content of vitamins B and G is low An important consideration therefore will be the matter of supplementing such diets with what is missing This can be accomplished by prescribing calcium phosphate, an iron salt and a suitable concentrate of vitamins B and G

CONCLUSIONS

The potassium content of the diet of patients with Addison's disease affects the course of the disease and the development of the symptoms of crisis

An intake of potassium not greater than 4 Gm a day, an amount comparable to that contained in a normal diet, may promote the excretion of sodium and chloride whereby significant losses of sodium and chloride occur and symptoms of crisis are precipitated. It may not be possible to prevent the occurrence of these effects of potassium with intakes of sodium and chloride as high as those provided by the administration of 18 Gm of sodium chloride and 5 Gm of sodium citrate daily.

If the intake of potassium is restricted to about 1.6 Gm a day, the requirement of sodium and chloride is materially diminished, and it becomes possible, although not necessarily desirable, to maintain patients with smaller doses of sodium salts than otherwise are needed and without injections of extract of adrenal cortex. Optimal therapeutic results demand not only the restriction of potassium but optimal rather than minimal doses of sodium salts and when possible, and certainly in emergencies, injections of an active extract of adrenal cortex.

The arranging of a diet which will contain not more than 1.6 Gm of potassium requires careful planning. Such a diet is likely to be inadequate in calcium, phosphate, iron and vitamins B and G. To avoid complications from deficiencies of these factors, the diet should be supplemented suitably by the addition of calcium phosphate, some iron salt and a concentrate of vitamins B and G.

ENDEMIC PNEUMONIA

PNEUMOCOCCIC TYPES AND THEIR VARIATIONS IN INCIDENCE
AND MORTALITY FOR ADULTS AND CHILDREN

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Classification of the types of pneumococci in endemic pneumonia was incomplete previous to and during the earliest part of our work. Originally group IV contained types IV to XXXII, and at least three different specific types were included in type II and two in type III. Since the more comprehensive classification of Cooper¹ and her co-workers has been accepted, the distribution of the types of pneumococci in endemic pneumonia has been studied in various parts of the world. These types have occurred in differing proportions, according to reports published in New York,² Boston³ and San Francisco⁴ and in Great Britain,⁵ Germany,⁶ Holland,⁷ India⁸ and South Africa⁹.

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From the Littauer Pneumonia Research Fund of the New York University College of Medicine, from the Medical Service, the Harlem Hospital (Department of Hospitals), and from the Research Laboratories (Department of Health) of the City of New York.

1 Cooper, G, Edwards, M, and Rosenstein, C. The Separation of Types Among the Pneumococci Hitherto Called Group IV and the Development of Therapeutic Antiserums for These Types, *J Exper Med* **49** 461-474 (March) 1929. Cooper, G, Rosenstein, C, Walter, A, and Peizer, L. The Further Separation of Types Among the Pneumococci Hitherto Included in Group IV and the Development of Therapeutic Antiserums for These Types, *ibid* **55** 531-554 (April) 1932.

2 Bullova, J G M. The Reliability of Sputum Typing and Its Relation to Serum Therapy, *J A M A* **105** 1512-1518 (Nov 9) 1935. Raia, A, Plummet, N, and Shultz, S. New Types of Pneumococci in the Pneumonias of Children, *Am J Dis Child* **42** 57-68 (July) 1931.

3 Heffron, R, and Varley, F. A Study of Lobar Pneumonia in Massachusetts. Methods and Results of Pneumococcus Type Determination, 1931-1932, *Am J Pub Health* **22** 1230-1248 (Dec) 1932.

4 Kohl, C, and Reitzel, R I. Type Specificity in Pneumonia and Pneumococcic Infection, *J A M A* **106** 1557-1561 (May 2) 1936.

(Footnotes continued on next page)

We have studied the 4,048 cases of endemic pneumococcic infection recorded during seven years, 1928 to 1935, at the Harlem Hospital. There were 2,708 cases of pneumonia in adults and 663 cases of pneumonia (primary) in children, a total of 3,371 cases¹⁰. In addition, there were 573 cases of adults and 204 cases of children suffering from bronchitis or acute infection of the upper respiratory tract, which in some instances simulated pneumonia when the patient was admitted to the hospital.

The methods of study have been outlined in our studies on bacteremia¹¹. In addition to the methods used for adults, the sputum of many of the children was obtained by means of the laryngoscope and in some cases by gastric aspiration. In most cases, however, pharyngeal swabbing, with incubation of the swab in broth, was carried out.

The patients were admitted to the Harlem Hospital to the service for patients with acute respiratory diseases of one of us (Dr. Bullowa) or to the pediatric service of Dr. Morris Gleich, who granted permission for the study of the children with pneumonia. The Harlem Hospital is a general municipal hospital located in the northeastern section of Manhattan Island, in the center of a population of about 250,000 Negroes. The district reached by ambulance includes also a large population of Puerto Ricans, Italians, Finns and Irish. The ambulance service is active, and according to the terms of the city charter it may not be refused to any patient who demands hospitalization. Patients are occasionally transferred to or from other hospitals. Accordingly,

5 Cowan, J. M., and others. Felton's Serum in Lobar Pneumonia, *Lancet* 2: 8-11 (July 2) 1932. Cruickshank, R. Felton's Serum in Lobar Pneumonia. Serological Typing of Pneumonia, *Tr. Roy. Med.-Chir. Soc. Glasgow* 25: 34-38, 1931.

6 Gundel, M., and Schwarz, F. K. Ueber die Typendifferenzierung und Epidemiologie der Gruppe X der Pneumokokken, *Ztschr. f. Hyg. u. Infektionskr.* 113: 498-522, 1932.

7 Vedder, A. Das Vorkommen der Pneumokokkentypen 4-32 in Amsterdam, *Acta brev. Neerland.* 3: 35-37, 1933.

8 Napier, L. E., and Dharmendra. Incidence of Pneumococcal Types in Pneumonia in Assam, *Indian M. Gaz.* 70: 181-185, 1935.

9 Lister, S., and Ordman, D. The Epidemiology of Pneumonia on the Witwatersrand Gold Fields and the Prevention of Pneumonia and Other Allied Acute Respiratory Diseases in Native Laborers in South Africa by Means of Vaccine, Publication 37, South African Institute for Medical Research, 1935, vol. 7.

10 Only cases of pneumonia due to a single classified pneumococcus have been included in our graphs and tables. Cases were omitted in which a second pneumococcus or other organism complicated the designation as well as cases of pneumonia due to an unclassified pneumococcus. The latter constituted 12 per cent of the cases of pneumococcic pneumonia recorded during the last four years.

11 Bullowa, J. G. M., and Wilcox, C. Incidence of Bacteremia in the Pneumonias and Its Relation to Mortality, *Arch. Int. Med.* 55: 558-573 (April) 1935.

one may say that the material included in the statistics is a random sample of the cases of pneumonia as they occurred from year to year and represents the endemic pneumonia and pneumococcic infections of the northern half of Manhattan Island and the lower portion of the Bronx

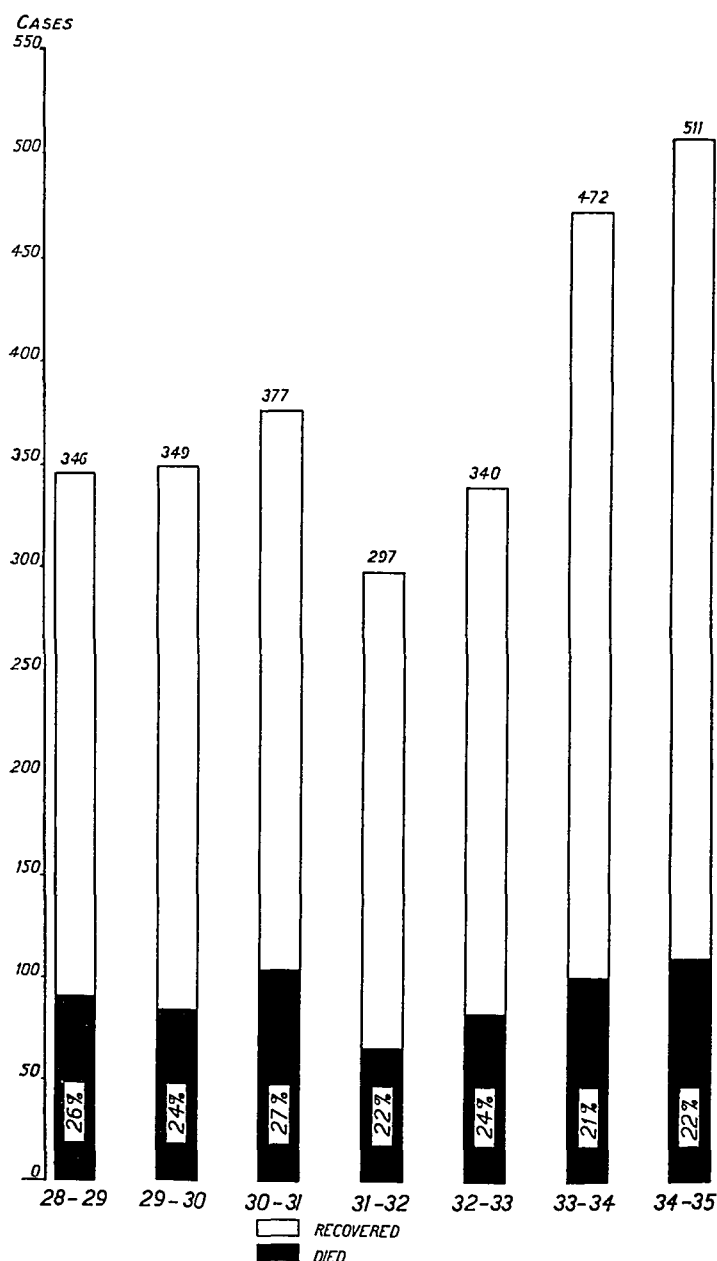


Chart 1—Summary of 2,708 cases of pneumococcic pneumonia in adults from 1928 to 1935. In charts 1 and 2 the black columns represent the patients who died and the white columns the patients who recovered.

The statistical year runs from July 1 to June 30, thus including an entire pneumonia season. The total number of patients admitted to the hospital year by year, together with the mortality percentages, is

graphically presented in charts 1 and 2. It will be observed that the mortality for adults varied from 24 to 27 per cent in the first three years, and in the four later years it varied from 21 to 24 per cent. During this period the mortality for children varied from 7 to 12 per cent in five of the seven years studied but reached 16 per cent in 1930-1931 and 20 per cent in 1932-1933. The year 1930-1931 which showed a high death rate (16 per cent) for children showed also a very high death rate for adults (27 per cent). In 1932-1933, when there were fewer cases in children, there was a high mortality for children (20 per cent). Previously and subsequently it did not exceed 16 per cent. There were a large number of cases of *Streptococcus haemolyticus* infection complicating pneumonia in the year 1930-1931.

The year by year variation in the percentage distribution of the various types of pneumococci and the combined percentage distribution

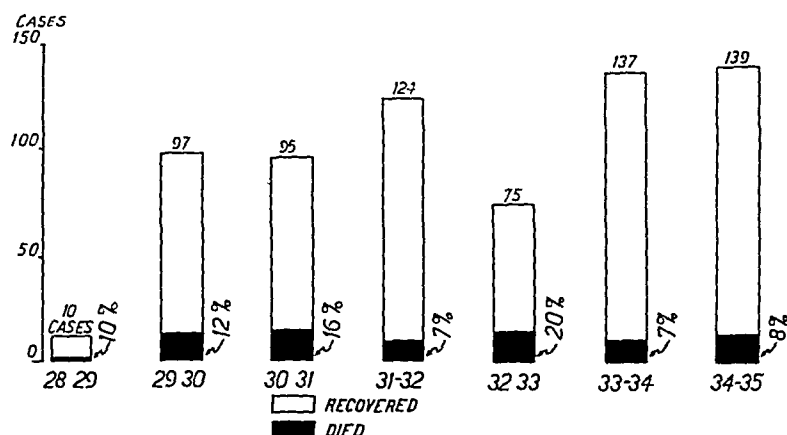


Chart 2—Summary of 663 cases of pneumococcic pneumonia in children from 1928 to 1935

for the seven years are shown in tables 1 and 2 for adults and children, respectively. In table 1 it is important to observe that type III pneumonia occurred slightly more frequently in adults than type II pneumonia and that types IV, V, VII and VIII were of almost as great importance from the standpoint of frequency as type II pneumonia. Though type II organisms produced the infection in 83 per cent of the cases of pneumonia in adults, they caused pneumonia in only 12 children (table 2).

Charts 3 to 5 for adults and charts 6 and 7 for children show the annual incidence of each type of pneumonia for a seven year period. It will readily be seen that from year to year the occurrence of the individual types of pneumonia varied widely. The marked fall in the total number of cases in 1931-1932 (chart 1) was reflected in the reduction in the total number of cases of type I pneumonia (charts 3 to 7). However, the marked increase in type I pneumonia in 1934-1935 was greater

ТАБЛ 1—*Pneumococcus Pneumonia in Adults from 1928 to 1936*

Type	1928 1925		1928 1929		1929 1930		1930 1931		1931 1932		1932 1933		1933 1934		1934 1935		1935 1936†	
	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%
I	725	23.7	108	20.3	98	23.8	99	23.8	71	22.1	92	24.3	116	23.8	141	27.1	127	19.9
II	256	8.4	52	9.8	48	11.6	36	8.7	27	8.4	31	8.2	32	6.6	20	5.8	32	5.0
III	297	9.7	36	6.8	22	7.8	51	12.2	31	9.7	32	8.5	60	12.3	55	10.6	70	10.9
IV	179	5.8	14	2.6	25	6.1	30	7.2	25	7.8	24	6.4	30	6.2	31	6.0	42	6.6
V	230	7.5	37	7.0	28	6.8	44	10.6	15	4.7	23	6.1	25	5.1	58	11.1	53	8.3
VI	61	1.7	5	0.9	7	1.7	1	0.2	10	3.1	10	2.6	13	2.7	5	1.0	8	1.3
VII	194	6.3	21	4.3	34	8.3	35	8.4	26	8.1	17	4.5	31	6.3	27	5.2	85	13.3
VIII	225	7.3	16	3.0	17	4.1	19	4.8	24	7.5	43	11.4	49	10.0	57	10.9	65	10.2
IX	69	2.2	14	2.6	6	1.5	9	2.2	12	3.7	8	2.1	10	2.1	10	1.9	18	2.8
X	17	0.6	1	0.2	7	1.7	1	0.2	0	0.0	4	1.1	3	0.6	1	0.2	3	0.5
XI	18	0.6	3	0.6	2	0.5	0	0.0	5	1.6	4	1.1	0	0.0	4	0.8	3	0.5
XII	32	1.0	5	0.9	3	0.7	5	1.2	2	0.6	2	0.5	12	2.5	3	0.6	14	2.2
XIII	31	1.0	7	1.3	9	2.2	2	0.5	2	0.6	1	0.3	4	0.8	6	1.2	1	0.2
XIV	87	2.8	7	1.3	2	0.5	11	2.7	10	3.1	13	3.4	26	5.3	18	3.5	31	4.8
XV	17	0.6	1	0.2	2	0.5	1	0.2	0	0.0	5	1.3	1	0.2	7	1.3	6	0.9
XVI	19	0.7	3	0.6	1	0.2	2	0.5	4	1.2	1	0.3	4	0.8	4	0.8	6	0.9
XVII	63	2.1	4	0.8	9	2.2	9	2.2	5	1.6	9	2.4	15	3.1	12	2.3	14	2.2
XVIII	40	1.3	2	0.4	6	1.5	5	1.2	3	0.9	3	0.8	9	1.8	12	2.3	15	2.3
XIX	33	1.1	2	0.4	5	1.2	5	1.2	4	1.2	5	1.3	5	1.1	7	1.3	10	1.6
XX	18	0.6	0	0.0	2	0.5	0	0.0	2	0.6	3	0.8	8	1.6	3	0.6	1	0.2
XXI	50	0.8	0	0.0	0	0.0	2	0.5	5	1.6	4	1.1	7	1.4	2	0.4	6	0.9
XXII	20	0.8	0	0.0	0	0.0	2	0.5	5	1.6	4	1.1	7	1.4	2	0.4	6	0.9
Total	2,621		341		343		367		283		334		460		493		610	
	3,066†		532†		411†		415†		321†		378†		488†		521†		639†	

* Types represented by less than 15 cases were omitted

† Total number of cases, including all cases of pneumococcus pneumonia (Cooper types) and X group and multiple infections

‡ Statistics for the year 1935 1936 became available after this paper was submitted for publication. There were 639 cases of pneumococcus pneumonia, showing an increase in the total incidence. Noteworthy is the proportional reductions of cases of types I and II and in the increase in the number of cases of types V and VII pneumonia, particularly type VII

ТАБЛ 2—*Pneumococcus Pneumonia in Children from 1928 to 1935*

Type	1928 1935		1928 1929		1929 1930		1930 1931		1931 1932		1932 1933		1933 1934		1934 1935	
	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%
I	120	16.0	1	3.5	12	9.5	19	18.8	20	15.2	6	7.6	38	26.8	24	17.2
II	37	4.7	2	6.9	1	0.8	4	4.0	7	5.3	9	11.4	4	2.8	8	5.8
III	98	5.1	0	0.0	8	6.3	5	5.0	6	4.5	3	7.8	10	7.0	6	4.3
IV	40	5.3	2	6.9	9	7.1	3	3.0	10	7.6	4	5.1	5	3.5	7	5.0
V	80	10.7	1	3.5	9	7.1	8	7.9	14	10.6	12	13.2	18	12.7	18	12.9
VI	18	2.3	0	0.0	3	2.4	6	5.9	3	2.3	2	2.5	4	2.8	0	0.0
VII	19	2.5	0	0.0	1	0.8	4	4.0	2	1.5	3	3.8	4	2.8	5	3.6
VIII	131	17.5	1	3.5	15	11.8	17	16.8	26	19.7	18	22.8	22	15.5	32	23.0
IX	39	5.2	0	0.0	8	6.3	5	5.0	9	6.8	4	5.1	6	4.2	7	5.0
Total	520		7		66		71		97		91		111		107	
	719†		29†		127†		101†		132†		79†		142†		139†	

* Types represented by less than 15 cases were omitted

† Total number of cases, including all cases of pneumococcus pneumonia (Cooper types) and X group and multiple infections

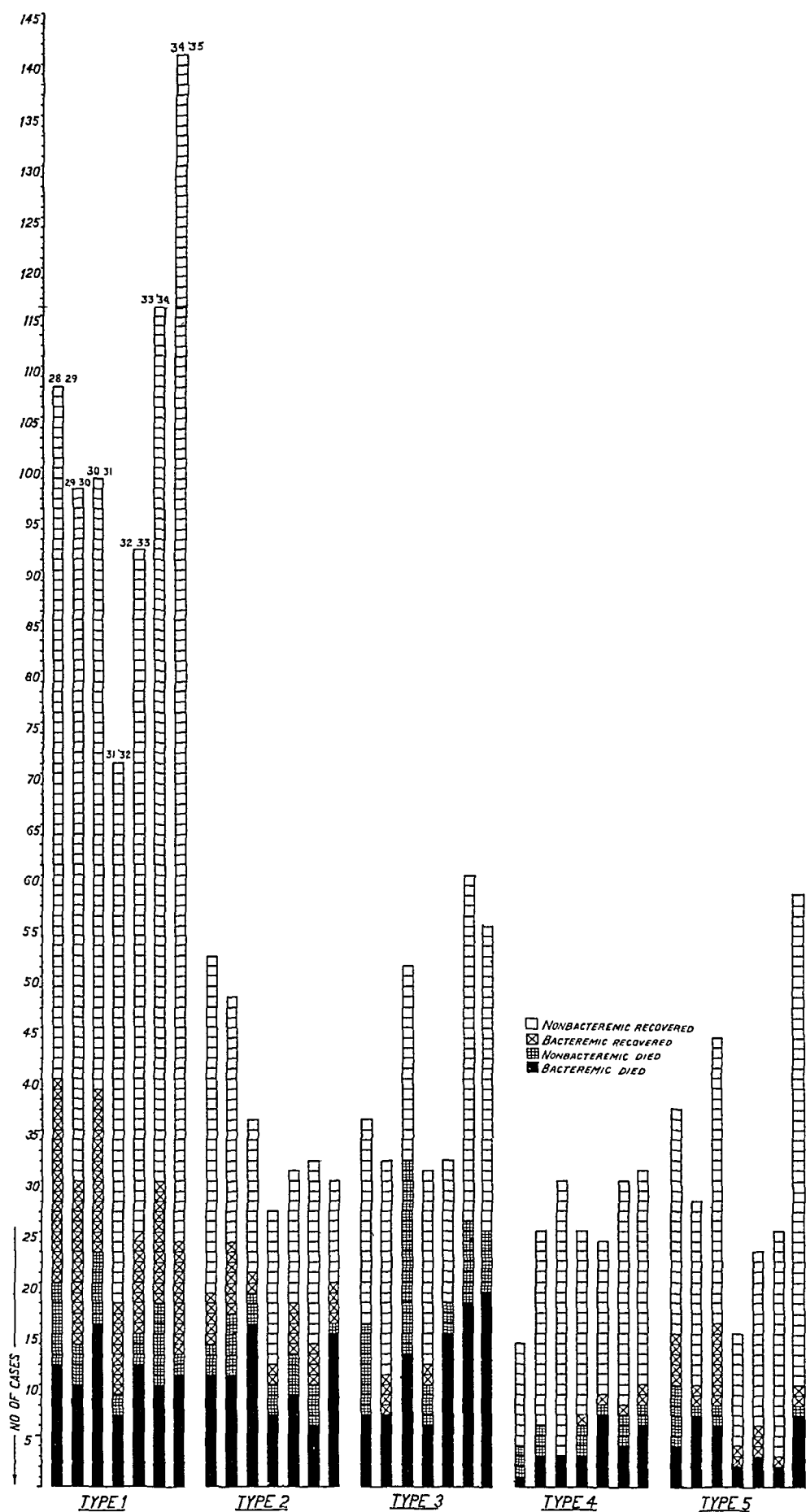


Chart 3—The yearly variations from 1928 to 1935 in the types of pneumonia in 2,708 adults

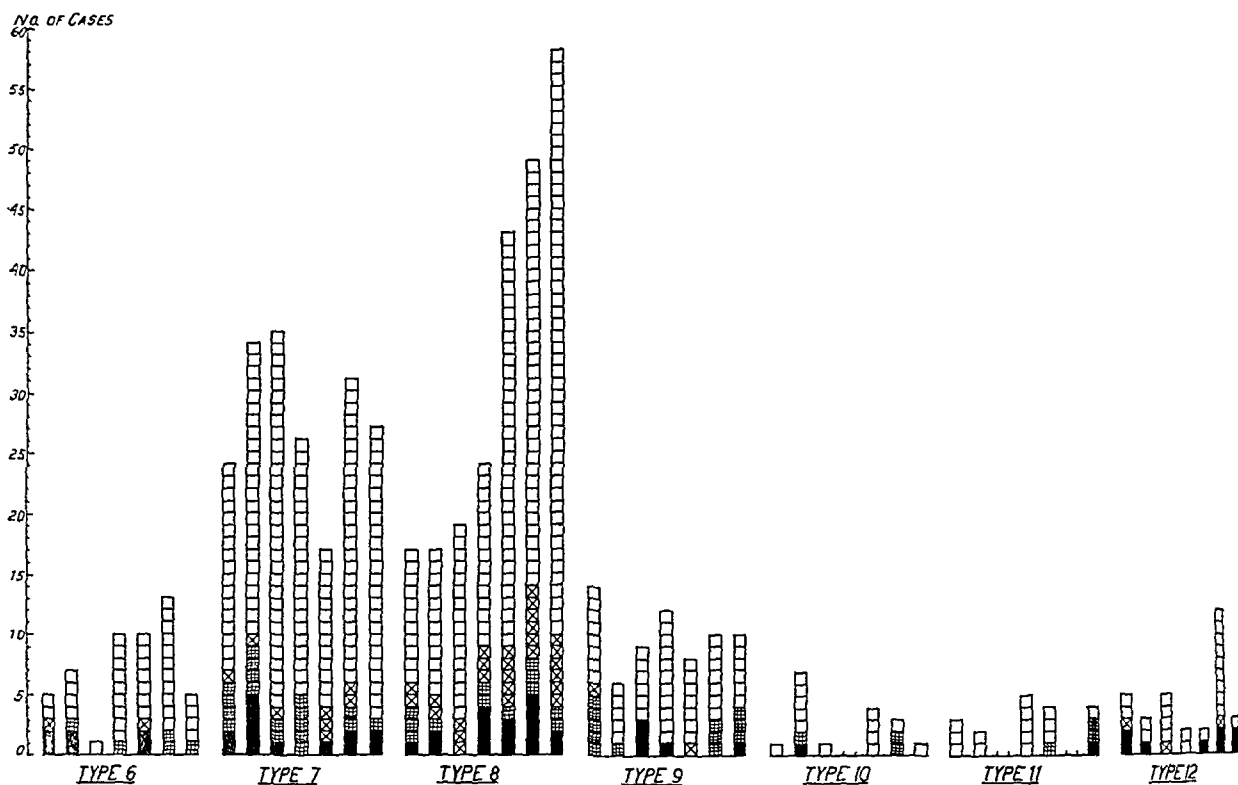


Chart 4—Chart 3 continued

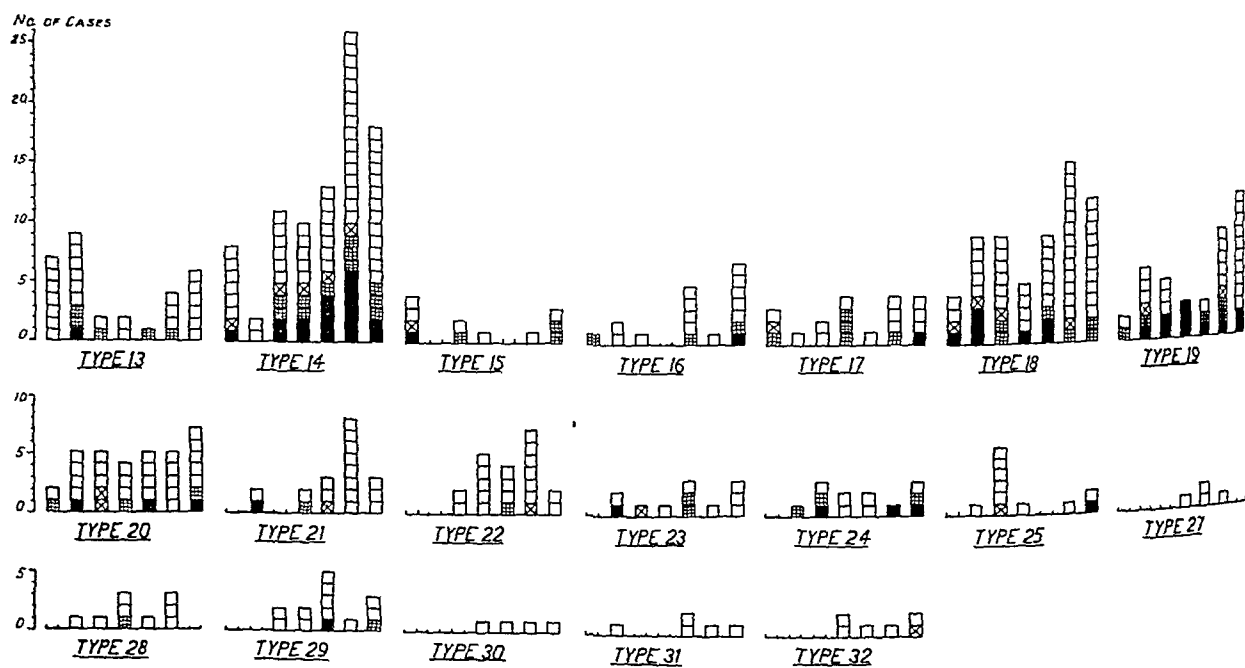


Chart 5—Charts 3 and 4 continued

No. OF CASES

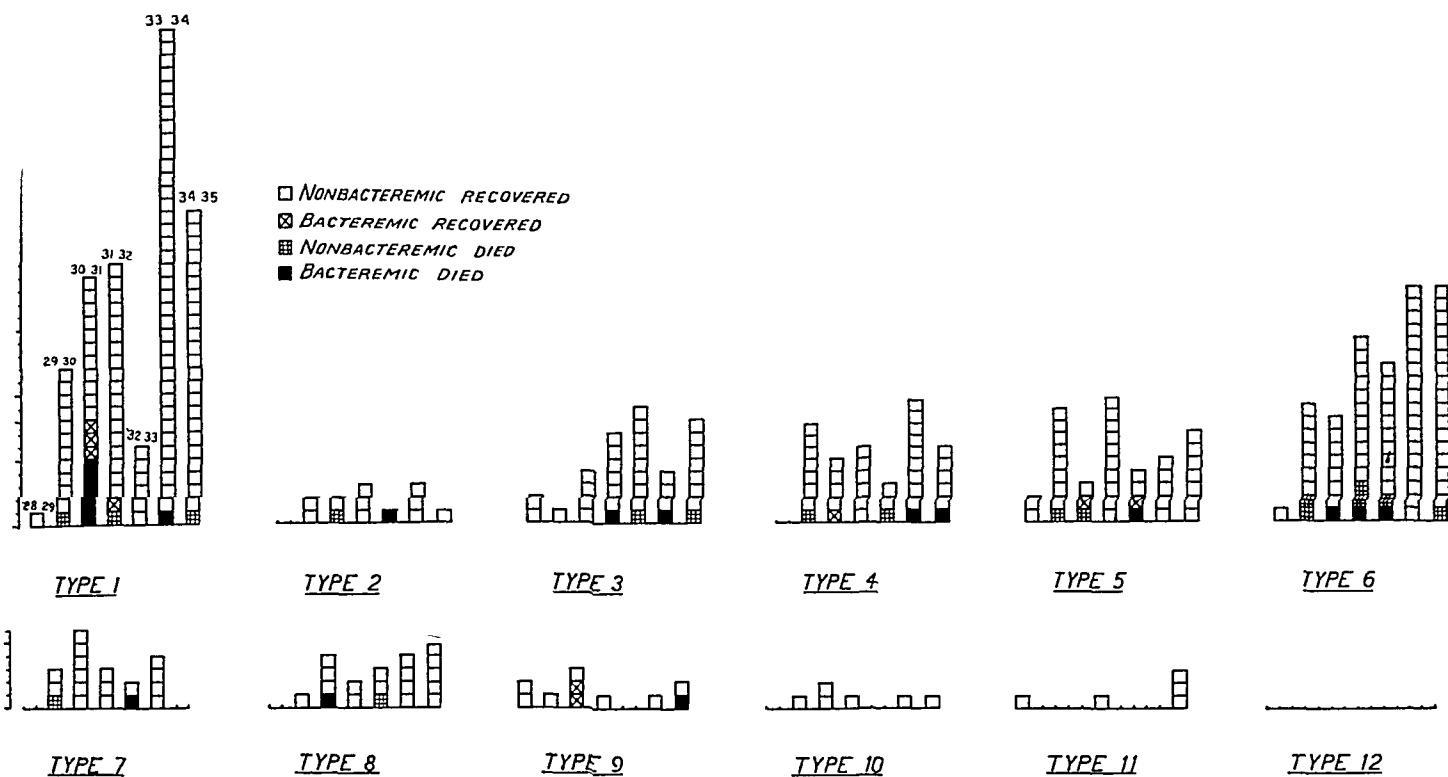


Chart 6—The yearly variations from 1928 to 1935 in the types of pneumonia in 663 children

No. OF CASES

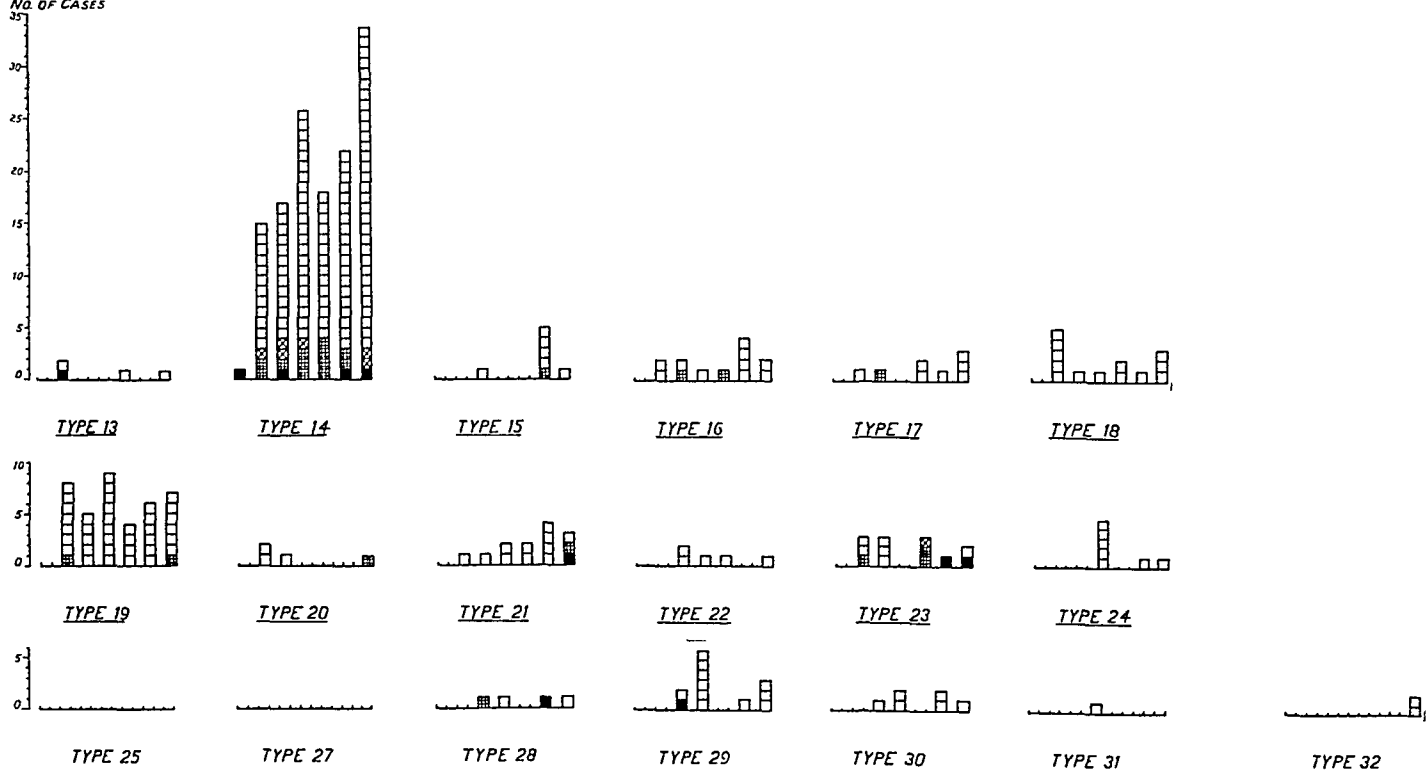


Chart 7—Chart 6 continued

than expected, with the prediction based on chart 1 It will be noted that while the number of cases of type I pneumonia increased, the number of cases of type II pneumonia decreased It must be noted also that type III pneumonia and especially type VIII pneumonia increased in frequency during the last two years Type V pneumonia, after

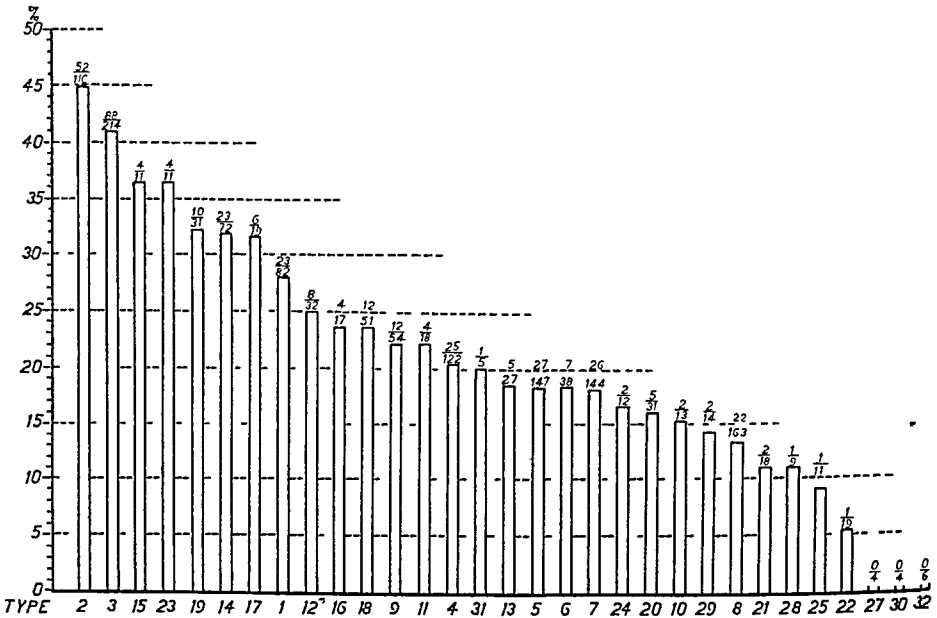
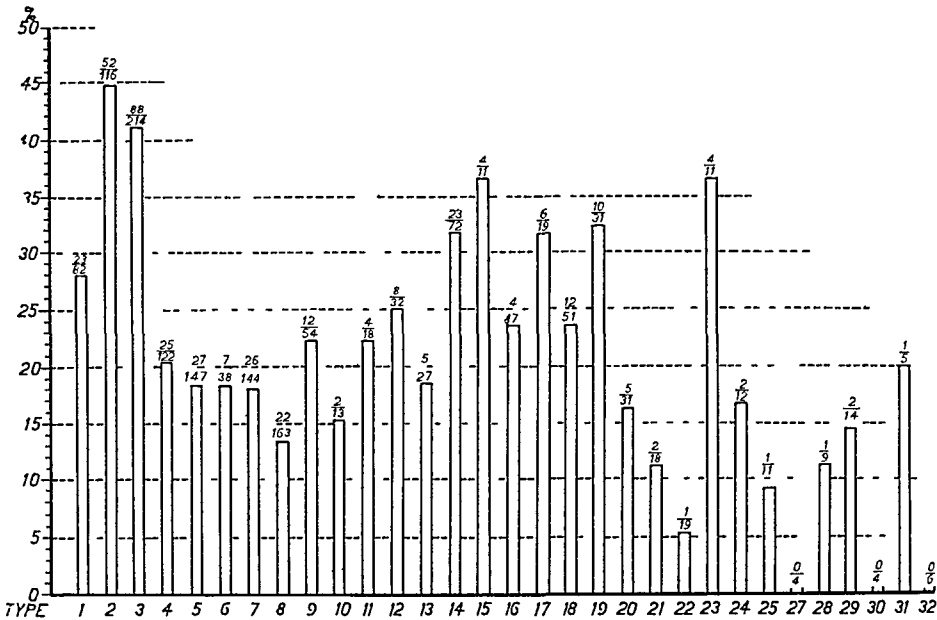


Chart 8—Mortality percentages in 1,515 cases (in adult patients) of pneumococcic pneumonia from 1928 to 1935 in which no serum was administered First the types are arranged in numerical order and then according to the mortality percentages

reaching an apparent maximum in 1931-1932, became infrequent until 1934-1935, when the frequency increased to a new high level Cases

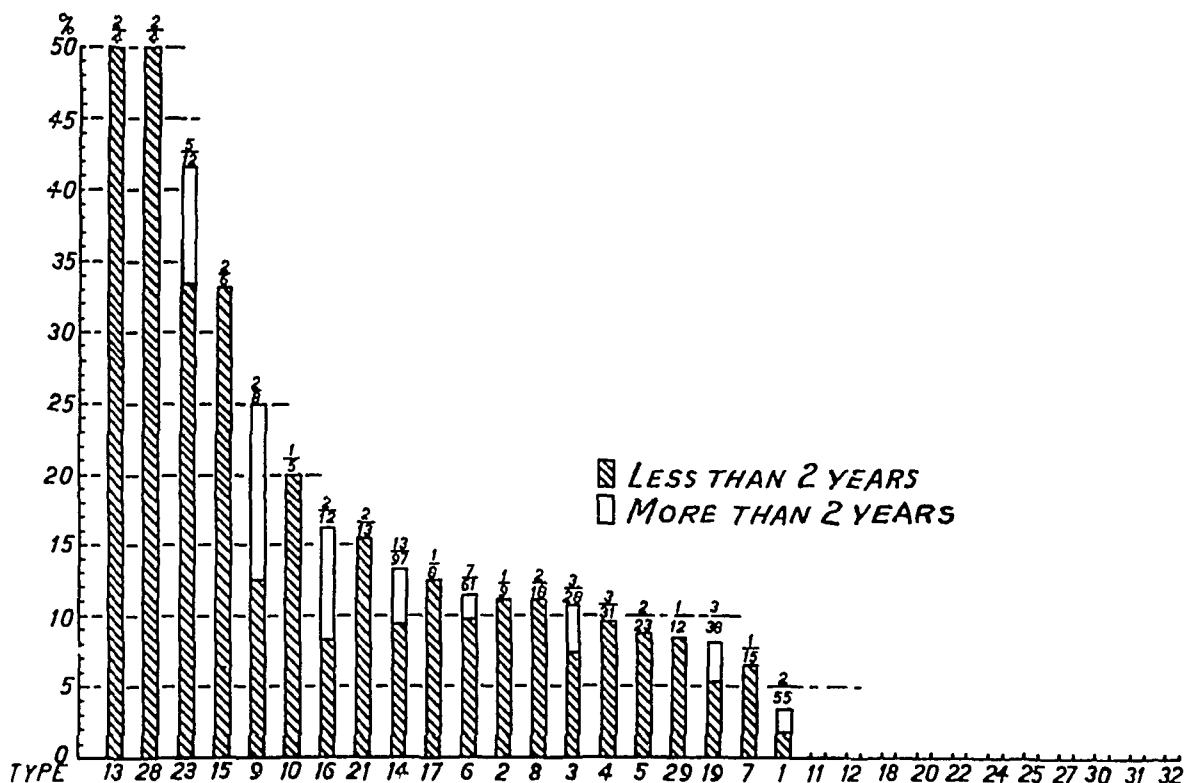
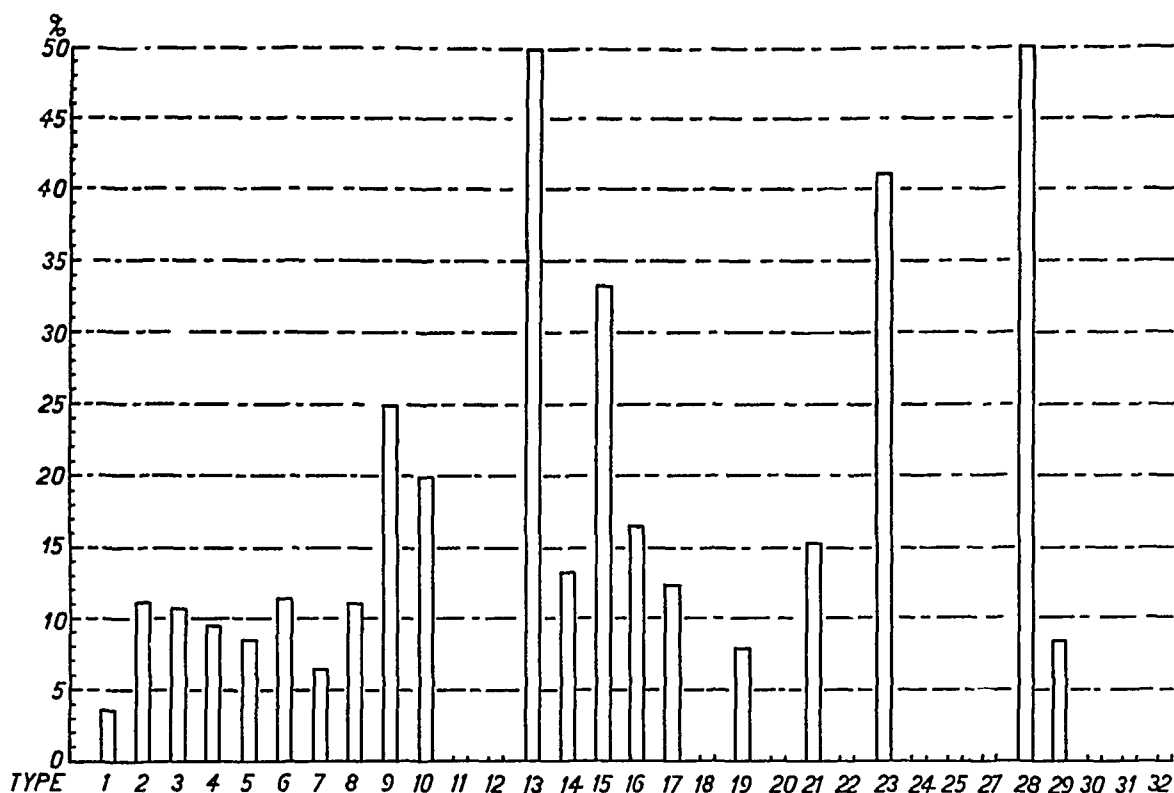


Chart 9—Mortality percentages in 498 cases (in children) of pneumococcic pneumonia from 1928 to 1935 in which no serum was administered. The lower portion of the chart shows the percentages for 264 children less than 2 years of age and for 234 children more than 2 years of age.

of the other types involved were too few to be considered separately. It may be observed, however, that though in adults the incidence of type III and type VIII pneumonia increased in the later years, this was not true for children.

The annual proportional distribution among the types is given in tables 1 and 2, which show that the various types of pneumococcic pneumonia varied in frequency from year to year. Charts 8 and 9 give information concerning the fatality of the different types, arranged numerically and also in the order of the fatality rate.

The various types of pneumococcic pneumonia varied markedly as to their fatality rates when serum treatment was not given. It is important to note that the cases may be grouped into those in which the mortality rate was more than 25 per cent and those in which it was less than 25 per cent. Some of the types of pneumonia for which serum is available are not among the most fatal types. Chart 9 shows that for only four of the types common to children was the mortality rate over 25 per cent. It may be seen also that eleven types did not cause death among children and that type I, which was eighth in order of frequency of fatality for adults, was least fatal for children. In adults types II, III, XV and XXIII were the most fatal. In children the fatal types were XIII, XXVIII, XXIII and XV. Type XXIII appeared to show a high mortality rate for both children and adults.

In addition to studying the annual variation in the types of endemic pneumococcic pneumonia, a study of the monthly occurrences of non-pneumonic pneumococcic infections of seven important types was undertaken for the year 1934-1935. It was thought that infections of the upper respiratory tract would precede the occurrence of pneumonia, and with this in mind the graph shown in chart 10 was prepared. In no instance did an observed infection of the upper respiratory tract of a given type precede the occurrence of pneumonia due to that type of organism. It is noteworthy that the different types of infection occurred at different times of the year and especially that type VIII infection occurred all through the pneumonia season, while type V was largely encountered during the late spring of the year studied.

There were 449 cases of nonpneumonic pneumococcic infection in adults during the seven year period. The most frequent infections were of types III, VI and VIII, as shown in chart 11. One of the types with a high fatality, type II infection, rarely appeared as a nonpneumonic infection, in spite of the frequency of this type as an incitant of pneumonia. In contrast, type III infection was fatal and frequent in pneumonia and was frequent also in nonpneumonic infections.

An entirely different series of types predominated among the non-pneumonic pneumococcic infections of the respiratory tract in children.

(chart 12) Types VI, XIV and XIX were the most important. Next were types XV and XVIII, which are of major importance in causing pneumonia.

Lister and Oldman have recorded that after vaccination of the laborers in certain mines of the Witwatersrand gold fields the types of

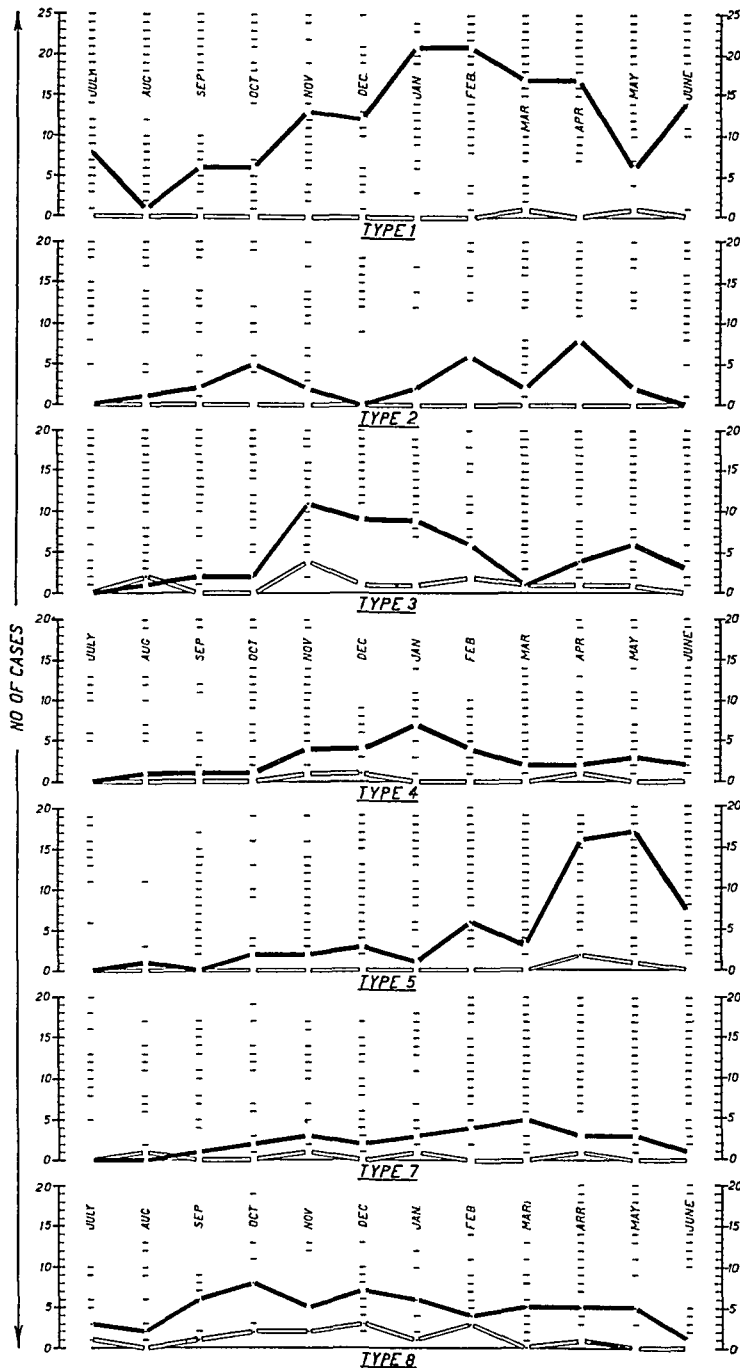


Chart 10—The monthly incidence in 1934-1935 of pneumonia and nonpneumonic infections of the respiratory tract of the common types. The black lines indicate pneumonic infections and the white lines nonpneumonic infections. Note the sharp rise in type V pneumonic infections in the spring months and that it was not preceded by a rise in the nonpneumonic infections.

pneumococci recovered in cases of pneumonia changed. They found that though the incidence of infections of the respiratory tract was unchanged, the mortality from pneumonia was materially reduced in the mines in which the workers had been vaccinated. The number of cases in which a pneumococcus was not isolated increased by two-thirds (from 11.6 to 31.2 per cent).

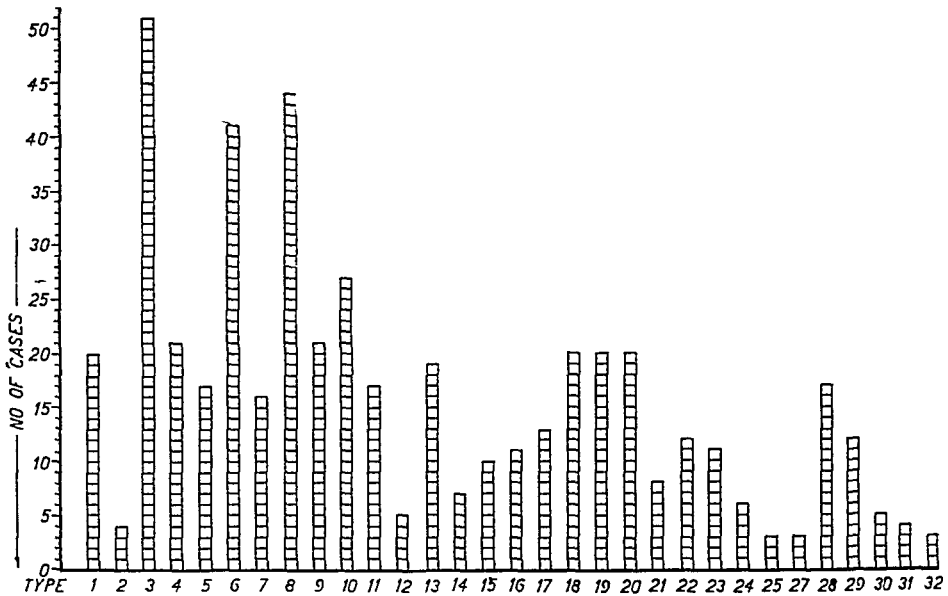


Chart 11—Types of nonpneumonic pneumococcal infections of the respiratory tract in 473 adults from 1928 to 1935

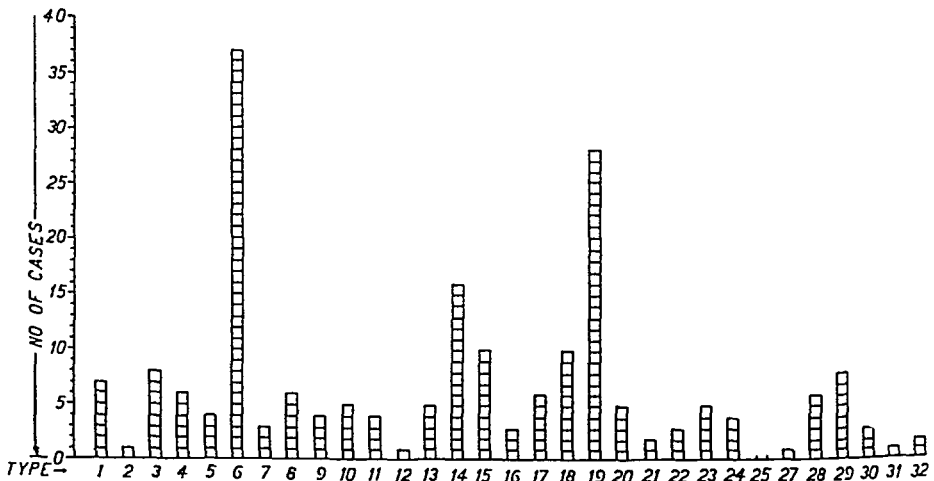


Chart 12—Types of nonpneumonic pneumococcal infections of the respiratory tract in 204 children from 1928 to 1935

In the communities where vaccination had not been carried out group B (our type II) pneumonia was the type most frequently found (31.6 per cent) and group C (our type I) was second (18.4 per cent). Group

E (our type III) became relatively more frequent in the communities where vaccination was performed (from 3.9 to 16.9 per cent). The vaccine used on the Witwatersrand was potent for our types I, II and III pneumococci and for a number of others (whether the latter were the same as the Cooper types is at present under investigation). The incidence of group C (our type I) pneumonia was diminished from 18.4 to 11.7 per cent by inoculation. By increasing the strength of the vaccine against group B (our type II) pneumococci, Lister and Oldman said that they were attempting to diminish the number of cases of pneumonia due to that pneumococcus.

CONCLUSIONS AND SUMMARY

The endemic pneumonias are a series of diseases which vary as to their occurrence from year to year and from month to month. They differ in respect to the age of the patients, incidence, mortality, tendency to invade the blood stream and other characters.

Whether the specific types of endemic pneumonia have individual cycles, as suggested by some of the graphs, can be determined only after the results of more studies similar to ours are available and after our own studies have been continued for a longer period. The results may justify immunization against the more fatal or more frequent types, so as to reduce the incidence of these infections. Such studies are required so that physicians and manufacturers may learn what types of pneumonia are prevalent and may require serum for treatment and vaccine for immunization.

There is a marked difference in the types of pneumonia among children and adults living in the same community, it remains for future investigations to determine the reasons for this difference.

PULMONARY CAPACITY IN LOBAR PNEUMONIA

WITH SPECIAL REFERENCE TO COLLAPSE THERAPY

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During the past several years artificial pneumothorax as a therapeutic measure in cases of lobar pneumonia has been enthusiastically employed. Initially pneumothorax was used empirically, and even at the present time the experimental data supporting the rationale of its use are meager (Lieberman and Leopold¹). The consensus² seems to be that the administration of artificial pneumothorax is a useful procedure in the treatment of unilateral lobar pneumonia when it is instituted early in the disease when there are no preexisting adhesions. The effect of this procedure in relieving the distressing symptoms of lobar pneumonia (pleuritic pain, dyspnea and toxic phenomena) has been described by most observers, and many have reported a critical fall in temperature (crisis) in approximately half the cases. The rationale for this procedure has not been subjected to extensive investigation, but the beneficial effects have been attributed to the following factors: (1) relief of pleural pain, (2) compression and immobilization of the acutely inflamed lung, (3) decrease in the absorption of toxins on the affected side due to the shunting of the blood flow from the affected to the unaffected side and (4) mobilization of the antibodies³.

Aided by a special grant from the Rockefeller Foundation

From the Department of Medicine, the School of Medicine and Dentistry, of the University of Rochester, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals

1 Lieberman, L M, and Leopold, S S. Therapeutic Pneumothorax in Experimental Lobar Pneumonia in Dogs, *Am J M Sc* **187** 315, 1934

2 (a) Leopold, S S, and Lieberman, L M. The Present Status of Artificial Pneumothorax in the Treatment of Lobar Pneumonia, *Ann Int Med* **9** 19, 1935
(b) Moorman, L J. Artificial Pneumothorax in the Treatment of Pneumonia. Report of Cases, *Internat Clin* **4** 119, 1934. (c) Blake, F G, Howard, M E, and Hull, W S. Artificial Pneumothorax in the Treatment of Lobar Pneumonia, *I A M A* **105** 1489 (Nov 9) 1935

3 Perlroth, S, and Topercer, M. Behandlung der Pneumonien mit kunstlichen Pneumothorax, *Wien klin Wchnschr* **45** 1508, 1932

The many stimulating reports (see Leopold and Lieberman²¹ and Blake, Howard and Hull²² for a review of the literature) on the treatment of lobar pneumonia by pneumothorax have led us to investigate the effects of this procedure on the respiratory function in this disease. The present study concerns the alterations in the vital capacity and other components of the total pulmonary capacity and the roentgenographic measurements during the induction of artificial pneumothorax in cases of typical lobar pneumonia.

METHODS AND MATERIAL

After the necessary preliminary examinations had been made and blood and sputum had been obtained for bacteriologic examination, a diagnostic roentgenogram of the chest was taken. When the patient's condition warranted it, roentgenograms were taken at both maximum inspiration and maximum expiration, according to the technic described by Hurtado and one of us (W. F.)⁴ From these roentgenograms the size and expansion of the chest could be followed throughout the course of the disease.

By the time the roentgenographic examinations were completed the prevailing type of organism in the sputum and the group of the pneumococcus had been determined by the *Quellung* method. The diagnosis being confirmed by roentgenograms and the etiologic agent being known, the patient was wheeled in a bed to a quiet room adjoining the laboratory, where measurements of the pulmonary capacity were made and artificial pneumothorax was induced.

Arterial blood was obtained from the radial artery and analyzed for the carbon dioxide and oxygen contents and the oxygen capacity by the method of Van Slyke.⁵

Next the expired air was collected for a two or three minute period in a Douglas bag. The number of respirations was counted. The gas was measured by means of a Sargent wet meter, and the volumes were reduced to standard. We found, as have others,⁶ that each patient invariably changes his type of breathing as soon as the mouth-piece is adjusted. The respirations become deeper and less frequent. Consequently, the values for the pulmonary ventilation are valueless and have been discarded. The temperature, pulse rate and respiratory rate charted in the accompanying figures were obtained from the nurses' records.

Measurement of the Pulmonary Capacity—The midcapacity (the amount of air remaining in the lungs at the end of normal expiration) was determined by the oxygen dilution method without forced breathing, as described by Christie.⁷ The length of the rebreathing period was seven minutes in all determinations. Duplicate determinations were usually made. The vital capacity was then mea-

4 Hurtado, A., and Fray, W. W. Studies of Total Pulmonary Capacity and Its Subdivisions. II Correlation with Physical and Radiological Measurements, *J. Clin. Investigation* **12** 807, 1933.

5 Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry. II Methods, Baltimore, Williams & Wilkins Company, 1932.

6 Binger, C. A. L., and Brow, G. R. Studies on the Respiratory Mechanism in Lobar Pneumonia. A Study of Lung Volume in Relation to the Clinical Course of the Disease, *J. Exper. Med.* **39** 677, 1924.

7 Christie, R. V. The Lung Volume and Its Subdivisions. I Methods of Measurements, *J. Clin. Investigation* **11** 1099, 1932.

sured graphically by means of a recording spirometer. The reserve and complementary volumes were measured separately. All determinations were made with the patient lying in bed with the head of the bed raised about 45 degrees. Binger and Brow⁶ said that such factors as pleuritic pain, anoxemia and general muscular weakness may easily impair the accuracy of measurements of the vital capacity. Fortunately in our experiments the patients who were selected proved to be cooperative, and we believe that the values for this capacity represent the true alterations produced by both the local and the systemic factors caused by acute febrile disease.

With the patient in the same position a needle was inserted in the second interspace in the midclavicular line. After the needle reached the intrapleural space, from 30 to 50 cc of air was injected, and the intrapleural pressure and the tidal volume were registered simultaneously by means of recording pens. The injection of air was then continued until a maximum of 500 or 600 cc was reached or until the expiratory pressure was slightly positive.

The patient was then returned to the division for nursing care and rest. Fluids were forced to 4,000 cc, and each patient received at least 10 or 12 Gm of sodium chloride per diem. In addition to the usual clinical records, the chloride content of the serum and the urinary excretion of chlorides were determined in most cases. Usually from six to eight hours elapsed before the patient was returned to the laboratory, where the aforementioned procedures were repeated, save for the arterial puncture. This process was continued until either the affected lung was collapsed or the crisis appeared. If the patient had preexisting adhesions, air was given until the mean intrapleural pressure equaled the atmospheric pressure.

After the crisis the determinations of the pulmonary capacity were made, and roentgenograms were taken at varying intervals. The examinations of the patients were repeated from one to six months after their discharge from the hospital. After complete recovery a roentgenogram was taken at maximum inspiration for the purpose of estimating the normal capacity.⁸

Owing to the many procedures and the critical condition of the patients, arterial blood and simultaneous records of the intrapleural pressure and the tidal volume were not obtained as frequently as was desired.

8 The regression formulas for the prediction of the normal capacity are as follows:

- 1 For males between the ages of 18 and 35

$$\text{Vital capacity in liters} = \text{roentgenographic volume of chest} (\times 0.24) + 1.22$$

$$\text{Total capacity in liters} = \frac{\text{vital capacity}}{78} \times 100$$

- 2 For males between ages of 35 and 60

$$\text{Total capacity in liters} = \text{roentgenographic volume of chest} (\times 0.38) - 0.17$$

$$\text{Vital capacity in liters} = \frac{\text{total capacity}}{100} \times 72.8$$

- 3 For females

$$\text{Vital capacity in liters} = \text{roentgenographic volume of chest} (\times 0.214) + 0.95$$

$$\text{Total capacity in liters} = \frac{\text{vital capacity}}{71.6} \times 100$$

During the past several years Hurtado and one of us (N L K) have had an opportunity to study two medical students and one patient from the outpatient department who became ill with pulmonary tuberculosis and were treated by artificial pneumothorax. In the case of one (C J) the pulmonary capacity was measured both before the onset of the disease and after the establishment of complete pneumothorax (left side). Each of the others was investigated only after collapse of the affected lung. These cases have been included in this study.

Since we are primarily interested in the disturbances in respiratory function during the course of lobar pneumonia and during collapse therapy and not in the therapeutic efficacy, the material was limited to cases of typical early unilateral lobar pneumonia of pneumococcic origin. In one case (T M) the pneumonia was of central type without complete lobar consolidation. Nine patients with pneumonia were studied, seven of whom were treated with artificial pneumothorax. There were two cases each of types I, III and XXXII, one each of types II and VII and one of group 4, the type being undetermined. The group included six men and three women, with ages ranging between 18 and 46 years. A brief review of the physiology of respiratory function during the induction of pneumothorax in a relatively healthy subject and during the course of lobar pneumonia is pertinent to an understanding of the alterations in the respiratory bellows during the insufflation of air in a case of pneumonia.

RESULTS

Alterations in the Pulmonary Capacity During the Induction of Pneumothorax in Relatively Healthy Subjects—Since artificial pneumothorax is usually unilateral, the alterations in the pulmonary capacity are complex. The vital capacity has been studied extensively during the establishment of pneumothorax, but the other components of the total capacity have been neglected. Most investigators⁹ have agreed that when a relatively normal lung is collapsed the decrease in vital capacity is not proportional to the amount of air injected. The initial insufflation causes a marked reduction in this capacity, but after several hours there is a slight increase. In subsequent inflations the same

9 (a) Anthony, A. J., and Heine. Spirographische Untersuchungen bei Lungenkollaps. I Mitteilung, Beitr z Klin d Tuberk **71** 362, 1929. (b) Bendove, R. A. The Vital Capacity in Artificial Pneumothorax. The Mechanism and the Factors Modifying the Vital Capacity, with Especial Reference to Its Clinical and Prognostic Value in the Collapse Therapy, Arch Int Med **36** 94 (July) 1925. (c) Gutman, S. Capacidad vital, Rev med latino-am **19** 34, 1933. (d) Kochs, K. Studien über die Vitalkapazität bei künstlichem Pneumothorax, bei Phrenicusexstirpation und einseitigem Brustheftpflasterverband, Beitr z Klin d Tuberk **73** 734, 1930. (e) Myers, J. A., and Bailey, W. Studies on the Respiratory Organs in Health and Disease. XX The Value of the Vital Capacity Test in Artificial Pneumothorax Treatment, Am Rev Tuberc **10** 597, 1925. (f) Schill, E. Pneumothoraxstudien. II Ueber den Zusammenhang von Vitalkapazität, Pneumothoraxdruck und Lungenkollaps bei mit Pneumothorax behandelten Lungenkranken, Beitr z Klin d Tuberk **65** 492, 1927. (g) Sieper, H. Die Vitalkapazität bei der Lungenphthise, besonders bei der Lungenkollapstherapie, ibid **65** 725, 1927.

quantity of air causes various diminutions in the vital capacity in the same subject. The complexity of changes in the vital capacity during the induction of pneumothorax has been variously attributed to the following factors: (1) the amount of air injected, (2) the intrapleural pressure (type of pneumothorax), (3) the structural and functional status of the affected lung, (4) status of the contralateral lung, (5) the stability of the mediastinum, (6) movements of the diaphragms and (7) the elasticity of the thoracic cage. An interplay of these factors can cause a multiplicity of alterations in the vital capacity and the other components of the total pulmonary capacity.

Obviously, alterations in the vital capacity cannot be interpreted without a knowledge of the volume of residual air. Because of the difficulties in measuring this volume, it has received little attention.¹⁰ Anthony and Heine¹¹ found that after unilateral pneumothorax the amount of residual air was diminished but that the diminution varied markedly. Furthermore, the variation was dependent not on the volume of the pneumothorax but on the rigidity of the mediastinum, alterations in the movements of the thoracic cage, the anatomic changes in the collapsed lung and a theoretical capacity designated by them as the "vital minimal volume." The normal capacity (midcapacity) was diminished, but the reduction was smaller than the volume of the pneumothorax. These investigators observed also that both the volume of the pneumothorax and that of the contralateral lung increased after the insufflation of air but that the increase of the latter was not so great as the increase of the volume of the pneumothorax.

The alterations in the pulmonary capacity following unilateral pneumothorax are shown in figure 1. In the first case (C J), in which there was complete pneumothorax of several months' duration on the left side, the total and vital capacities and the midcapacity were moderately reduced, being 68, 57 and 68 per cent, respectively, of the predicted capacity. The amount of residual air was actually higher than the predicted value and only slightly less than that found before the establishment of pneumothorax.

In the second patient (J K) the right lung was collapsed about 70 per cent. The measurement of the pulmonary capacity was made three hours after a refill was given. The intrapleural pressure at that time was -4 cm. of water at the end of normal inspiration and atmospheric (0 cm. of water) at the end of expiration. Here again,

¹⁰ Wolf, H. J. Die nervöse Atmungsregulation bei der Lungentuberkulose. III. Der Einfluss des künstlichen Pneumothorax auf den Ausfall der Funktionsprüfung der Atmung und auf das Verhalten der Lungenvolumina, *Ztschr. f. d. ges. exper. Med.* **63**: 616, 1928.

¹¹ Anthony, A. J., and Heine. Spirographische Untersuchungen bei Lungenkollaps. II and III. Mitteilung, *Beitr. z. Klin. d. Tuberk.* **73**: 51, 1929, footnote 9a.

the total and vital capacities and the midcapacity all were proportionally reduced, approximately 40 per cent, while the amount of residual air was 56 per cent of that predicted

The results in the third case (D F) were similar to those in the first. The determination of the pulmonary capacity was made several days after the last refill was given, at which time the intrapleural pressure was -4 cm of water at normal inspiration and 0 cm of water at expiration. The left lung was collapsed about 80 per cent. There was a reduction of from 50 to 55 per cent in the total and vital capacities and the midcapacity, while the amount of residual air was 65 per cent of that calculated.

In these cases all the values for the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ were slightly increased, owing to a greater reduction in the vital capacity than in the volume of residual air. Likewise, the values for the ratio $\frac{\text{midcapacity}}{\text{total capacity}} \times 100$ were slightly elevated. There was no disturbance,

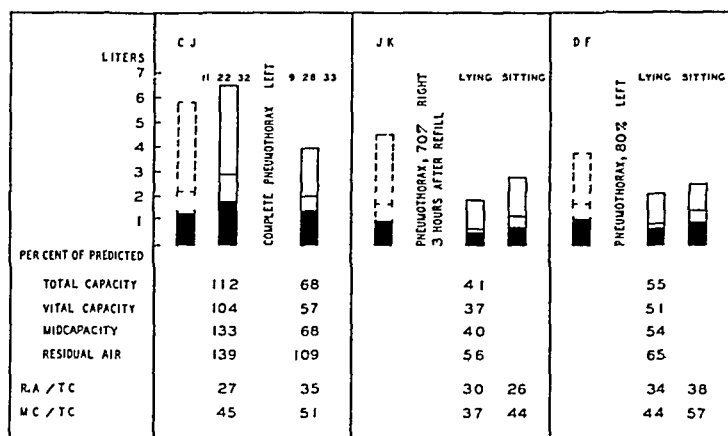


Fig 1—Predicted and observed pulmonary capacities in patients with unilateral pneumothorax. The columns with broken lines represent the predicted values, while the ones with solid lines represent the observed pulmonary capacity. In this and subsequent figures the black area represents the residual air and the white space above represents the vital capacity. The line dividing the vital capacity is the level of the midcapacity.

however, in the components of the vital capacity, the complementary air comprising approximately 80 per cent of the vital capacity.

Anthony and Heine¹¹ found that the alterations in the vital capacity due to a change in posture in persons with pneumothorax were similar to but not as marked as the changes in normal subjects. The effect of posture was studied in two of our patients (fig 1). When the subject assumed a sitting position there was a marked increase in the total and vital capacities and the midcapacity and in the amount of reserve air. There was a moderate increase in the amount of residual

Radiographic Measurements

Patient	Lung Affected	Number of Days After Onset	Stage of Disease	Amount of Air, Cc	Diaphragm at Maximum Inspiration				Area of Pulmonary Fields, Maximum Inspiration, Sq Cm	Area at Maximum Expiration	Move Maximum Inspiration of Rib, Degrees	Ordinate Measurements	
					Right		Left					Area, Sq Cm	Transverse Diameter, Cm
					Height, Cm	Excursion, Cm	Height, Cm	Excursion, Cm					
Pneumothorax in Early Pulmonary Tuberculosis													
C F	Left, complete collapse	Before collapse	23 1	16	25 1	58	652	69 3	21				
		After collapse	25 3	7 7	25 6	0 1	630	73 9	Right 22 Left 7				
J K	Right, 70% collapse	After collapse	15 8	—2 7	23 2	1 7	518	80 5					
D F	Left, complete collapse	After collapse	18 6	2 3	21 2	1 0	413	77 6					
Lobar Pneumonia													
W A	Right	Consolidation	21 8	0 6	21 9	3 9	571	73 2	Right 0 Left 21			116	13 1
		Partial resolution	20 6		24 7		527					137	13 6
		Complete recovery	22 7	5 4	25 6	5 5	580	62 1	Right 21 Left 20			121	12 8
L G	Right	Consolidation	22 4		26 0		670					180	15 9
		Spread	23 0		25 6		680					185	15 7
		Complete resolution	23 8	5 7	26 7	7 2	696	65 9	19			168	15 6
		Complete resolution	25 6	6 0	27 8	7 1	745	61 3	16				
Lobar Pneumonia Treated by Collapse Therapy													
3	Right	Consolidation										140	10 1
4			500	25 2	25 8		651				136	13 1	
6		Spread of pleural pain	300	23 3	23 1		580				136	12 9	
12		Clearing		25 8	26 0		680				123	11 9	
37	Recovery		23 7	1 6	25 7	1 9	663	64 7	22		102	11 1	

E L Right	3	Consolidation		19 0	22 5	131	123	12 4
	3		700	18 3	22 8	462		
	1		450	18 9	22 1	480	121	12 8
	4		350	19 1	23 1	502		
	6						127	13 2
	9			22 3	21 1	514	105	11 8
	19	Resolution		22 6	23 1	539	107	12 6
	48	Recovery		20 5	21 9	487	65 3	22
	111	Recovery		20 0	21 0	460	68 0	23
	3	Central consolidation					105	11 3
O M Left	4	Spread		23 3	24 6	648	68 7 Right 20 Left 15	122 12 5
	5		650	21 3	23 3	575	127	13 0
	6		650	19 5	21 6	535		
	11	Partial resolution		22 3	22 6	600	126	13 3
	49	Recovery		23 7	25 0	650	66 8	20
	58	Recovery			4 4			11 9
	2	Consolidation		20 7	22 6	510	98	11 8
	3		500	22 1	24 2	610		
	4		300	22 3	21 8	587	140	14 2
	46	Recovery		20 1	22 0	539	63 8	20
I G Left	3	Pleural pain		18 0	18 2	410	112	12 1
	15		350		0 8			
	101	Recovery		16 6	2 2	410	77 5	13
M L Right	2	Pleural pain		17 4	22 4	445		
	3		500	16 6	22 1	489		
	3		500	17 5	22 4	455		
	4		500	19 5	24 2	510		
	5		350	19 4	24 1	510		
	48	Recovery		17 8	22 3	482	63 3	22
	111	Recovery		17 7	21 3	468	65 8	25
	2	Consolidation		22 0	26 4	512	80 5	8
W H Right	3		500	23 0	25 3	551		

air while the change in the amount of complementary air varied. The percentage of change was similar to that found in normal persons¹².

The size of the chest (the area of the pulmonary fields) in one case (C J) was essentially the same after the injection of air as before, but in all cases the ability to expand the thorax was markedly diminished (table). The excursions of the diaphragm and the rotation of the ribs were greatly reduced on the affected side, while on the opposite side they were actually increased.

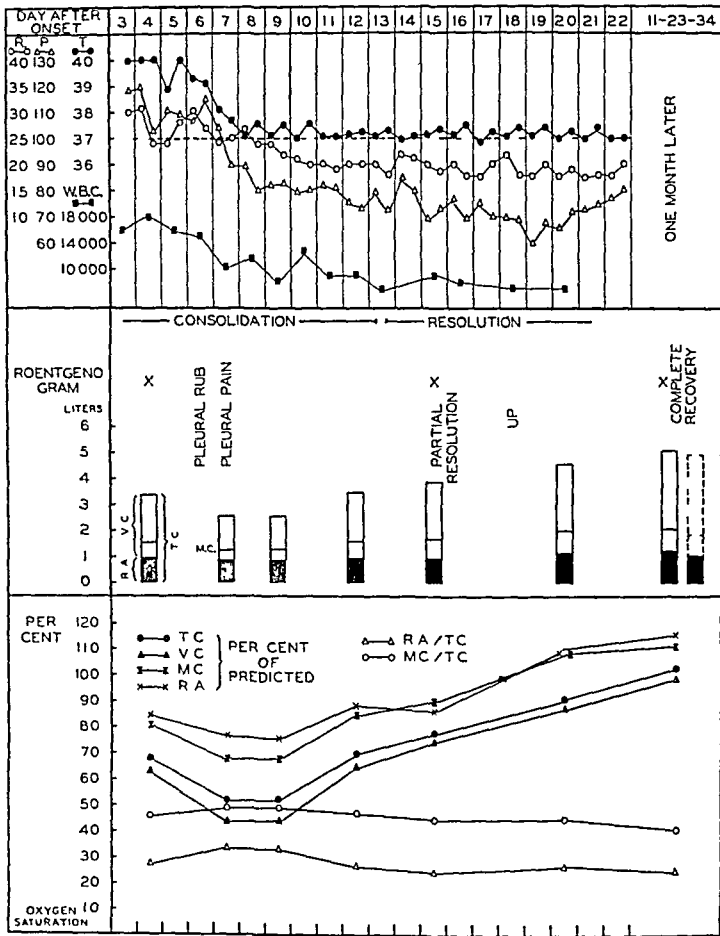


Fig 2—Predicted and observed pulmonary capacities during the course of lobar pneumonia. In this and subsequent charts the symbols (in the lower division) for the various absolute and relative values of the pulmonary capacity are identical. The column with broken lines at the extreme right represents the predicted values for the pulmonary capacity. At the left are recorded the respiratory and pulse rates, the temperature in degrees centigrade and the leukocyte count. This patient, W A, a man aged 22, was admitted to the hospital on Oct 7, 1934, and was discharged on October 26. In this case and in all the other cases in this series culture of the blood was sterile. The lower lobe of the right lung was the site of pneumonia due to type VII pneumococci.

12 Hurtado, A, and Fray, W W. Studies of Total Pulmonary Capacity and Its Subdivisions. III Changes with Body Posture, J Clin Investigation 12 825, 1933.

Alterations in the Pulmonary Capacity During the Course of Lobar Pneumonia—According to the observations of Myers¹³ and Arnett,¹⁴ soon after the onset of lobar pneumonia the vital capacity is reduced tremendously. The maximum reduction is reached near the day of the crisis, and the increase in this capacity is the first evidence of resolution. Eventually there is a return of the vital capacity to the prepneumonic level, unless pleural adhesions are present to prevent it. Furthermore, there is no parallelism between the extent of the pulmonary lesion and the reduction in the vital capacity (Myers¹³ and

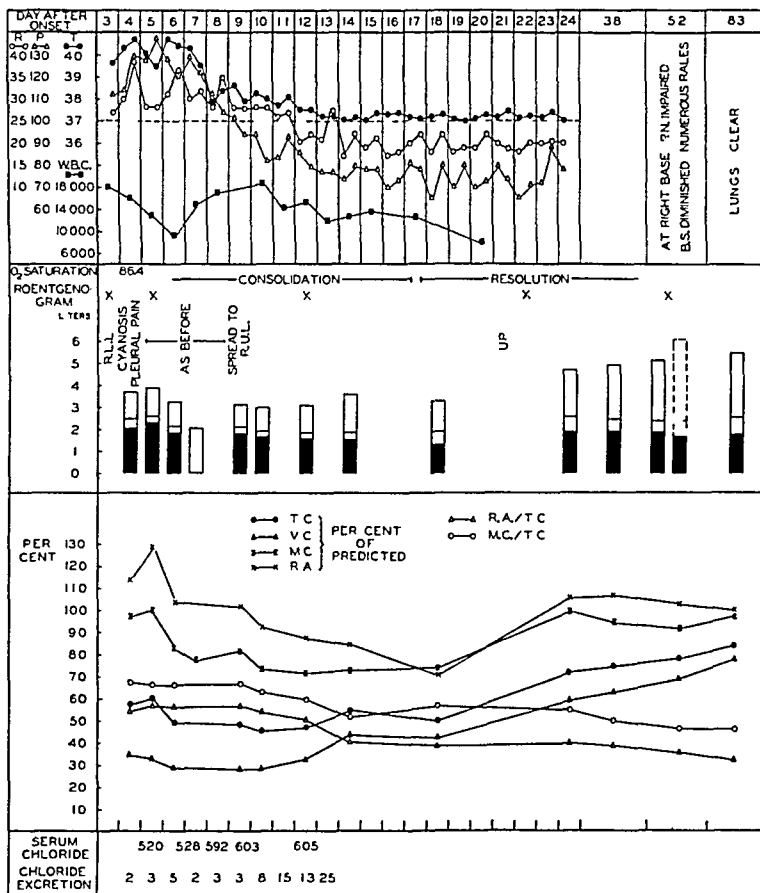


Fig 3—Observed pulmonary capacity during the course of lobar pneumonia. The serum chloride content is expressed in milligrams per hundred cubic centimeters and the amount of sodium chloride excreted per diem in grams. The blood for these determinations was collected under oil without stasis by the resident physicians of the hospital, and the analyses were made by technicians in the clinical laboratory. This patient, E G, a man aged 42, was admitted to the hospital on March 18, 1935, and was discharged on April 8. The upper and lower lobes of the right lung were the site of pneumonia due to type II pneumococci.

13 Myers, J. A. *The Vital Capacity of the Lungs*, Baltimore, Williams & Wilkins Company, 1925.

14 Arnett, J. H. *Vital Capacity of the Lungs—Changes Occurring in Health and Disease*, J. Clin. Investigation **14**: 543, 1935.

Anthony¹⁵) Bingei and Biow⁶ found that a "constant relationship existed between the persistence and disappearance of symptoms and fluctuations of the functional residual air. This capacity was diminished during the persistence of pathological signs in the lungs, and returned to normal as the pathological signs disappeared." Measurements of the volume of residual air during lobar pneumonia have been made in only a few cases¹⁵ Usually it is reduced but not in proportion to the pulmonary involvement. The degree of diminution in the volume is influenced by a number of factors, which will be discussed later.

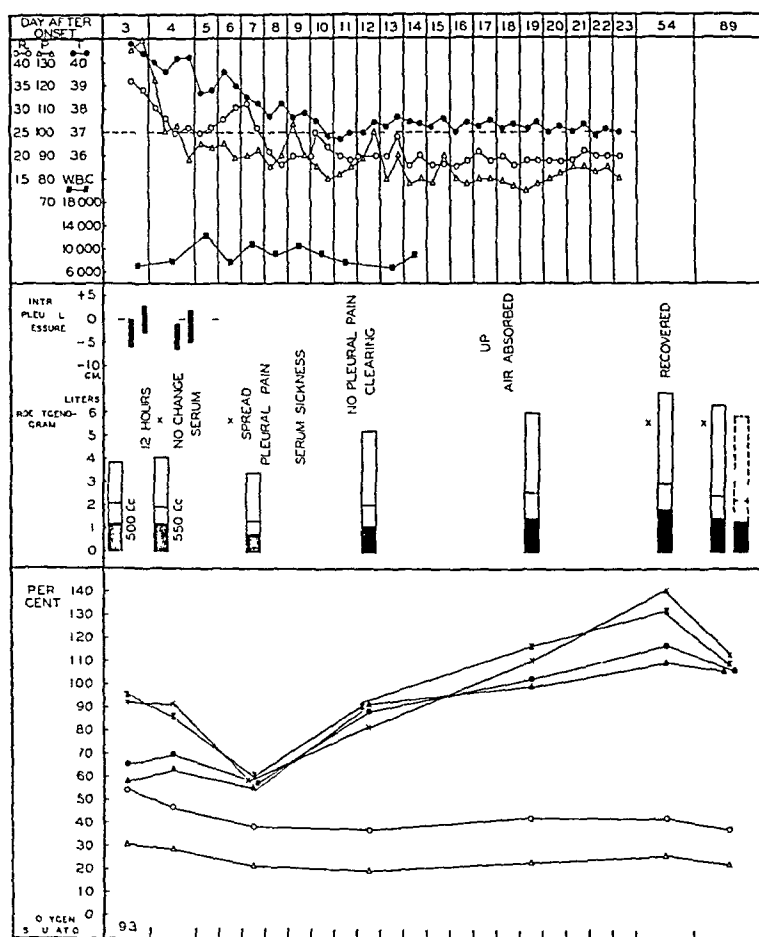


Fig 4—This patient, A D a man aged 21, was admitted to the hospital on Oct 15, 1934, and was discharged on November 4. The lower lobe of the right lung was the site of pneumonia due to type I pneumococci.

The values for the total pulmonary capacity and its subdivisions during the course of lobar pneumonia are presented in figures 2 and 3. Observations in seven cases prior to the insufflation of air in the pleural

15 Anthony, A J Untersuchungen über Lungenvolumina und Lungenventilation. Deutsches Arch f klin Med **167** 129, 1930.

cavity are shown in figures 4 to 10. Early in the course of the disease (from the second to the fourth day after the onset) the vital capacity was markedly reduced (from 35 to 65 per cent of the predicted values) in all cases. There appeared to be no general relationship between the extent of the pulmonary involvement and the reduction in this capacity. However, several patients (E G, E L, I G and M L) who complained of pleuritic pain showed a greater reduction in this capacity than those who did not complain of this type of pain. Interestingly, in one patient (W A) pleural pain developed on the seventh day of the disease, and the vital capacity fell from 63 to 44 per cent of the predicted value.

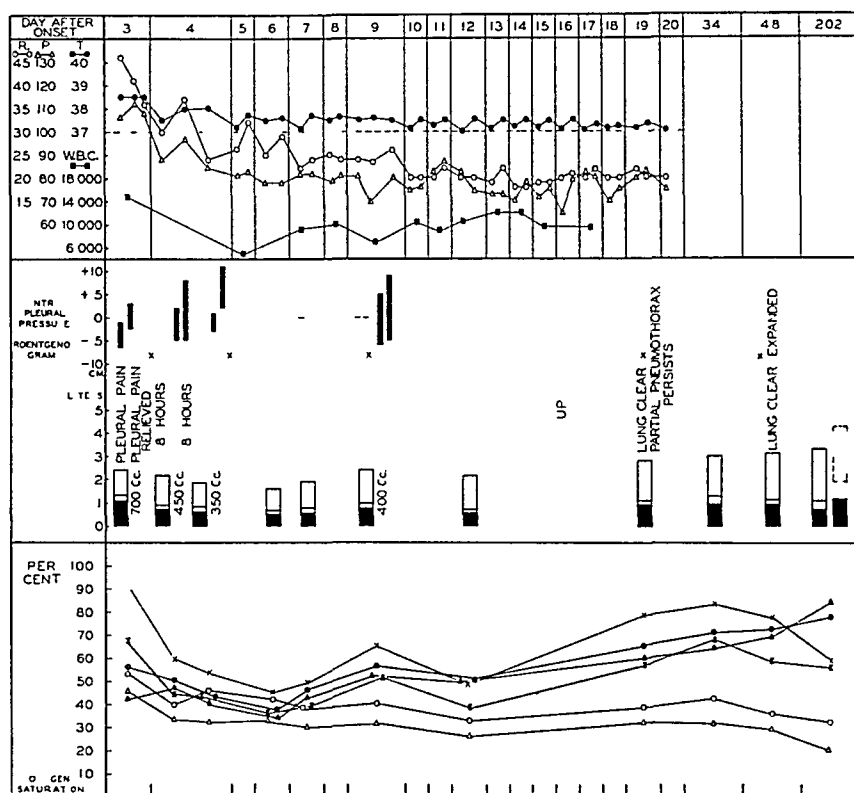


Fig 5—This patient, E L, a woman aged 45, was admitted to the hospital on Oct 27, 1934, and was discharged on November 13. The middle and lower lobes of the right lung were the site of pneumonia due to type IV pneumococci.

The alterations in the residual air during the early stages of lobar pneumonia were variable. There was a slight reduction (from 68 to 92 per cent) of this capacity in three patients (W A, A D and T M), while in the remainder the amount of residual air was actually increased. Similar observations were found with regard to the mid-capacity, except that the reduction was more marked. The greater diminution in the midcapacity than in the amount of residual air may

have been due to changes in the volume of reserve air, but it was found that the latter volume constituted a normal percentage of the vital capacity

There was a reduction in the total capacity (from 55 to 80 per cent), but not so marked as that in the vital capacity, owing to the relative increase in the amount of residual air. Pleural pain likewise influenced the diminution in this capacity.

The relative values are of great interest in these cases. Because of the relatively greater reduction in the vital capacity than in the amount

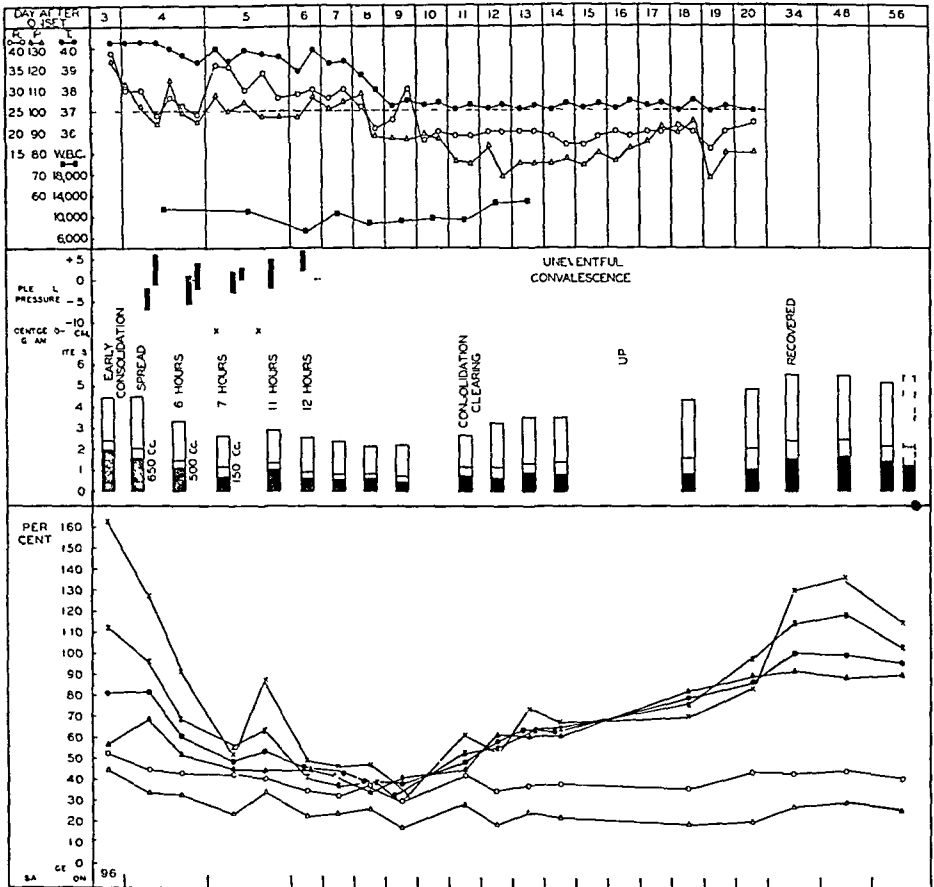


Fig 6—This patient, C M, a man aged 18, was admitted to the hospital on Dec 11, 1934, and was discharged on December 28. The upper lobe of the left lung was the site of pneumonia due to type III pneumococci.

of residual air, the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ was increased in all patients except one (T M). This patient had a central type of pneumonia. A similar but less marked change was found in respect to the ratio $\frac{\text{mid-expirity}}{\text{total capacity}} \times 100$.

The measurements of the pulmonary capacity were followed throughout the course of the disease in two cases (figs 2 and 3). As

the disease progressed all the absolute values were further decreased. This continued until the crisis, when they remained stationary for several days and then gradually returned to the predicted values within a period of one or two months after the onset of the disease. The return was gradual and never complete in one case (E G), owing probably to thickening of the pleura at the base of the right lung. A spread of the consolidation to another lobe (E G) further reduced the absolute values for all the components.

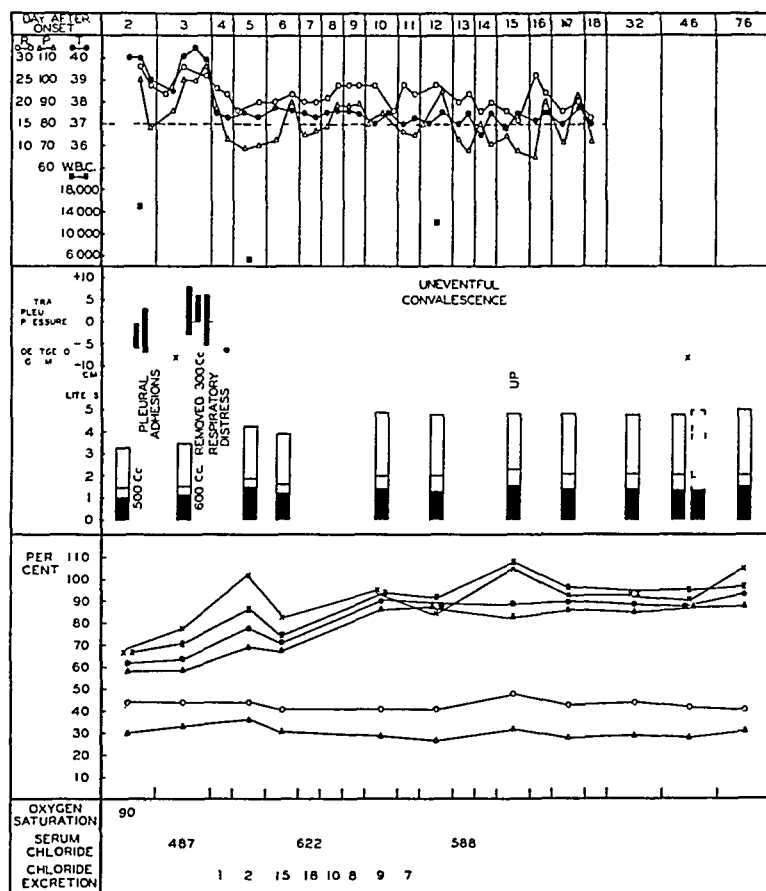


Fig 7—This patient, T M, a man aged 45, was admitted to the hospital on Dec 18, 1934, and was discharged on Jan 3, 1935. The upper lobe of the right lung was the site of pneumonia due to type III pneumococci. There was pulmonary fibrosis throughout both pulmonary fields.

Details of the roentgenographic measurements are charted in the accompanying table. During the stage of consolidation there was a marked reduction in the patient's ability to expand the chest, as evidenced by alterations in the values for the excursions of the diaphragm, movement of the ribs and the ratio $\frac{\text{area at maximum expiration}}{\text{area at maximum inspiration}} \times 100$. Similar alterations in the movement of the ribs and diaphragm have been

observed by Jung and Van Allen¹⁶ The level of the diaphragm at maximum inspiration was generally higher on the involved than on the contralateral side As the process in the lung resolved the height of the pulmonary field increased Since the two sides of the thorax cannot act absolutely independently, these changes were reflected to a lesser degree on the opposite side The area of the pulmonary fields (including the cardiac area) increased somewhat as the patient convalesced Both the area and the transverse diameter of the heart were

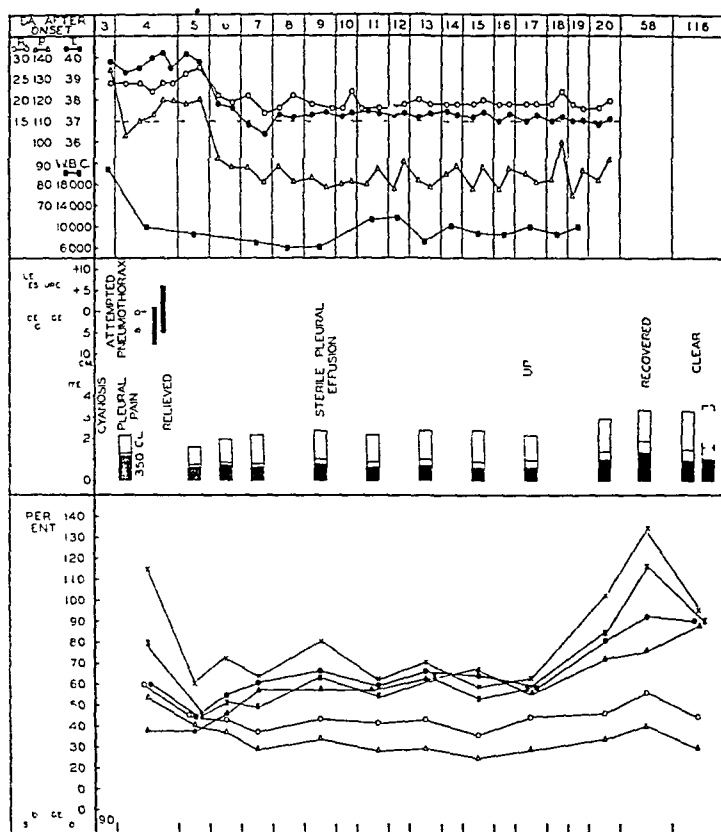


Fig 8—This patient, I G, a woman aged 29, was admitted to the hospital on Jan 4 1935, and was discharged on January 21 The lower lobe of the left lung was the site of pneumonia due to pneumococci of group 4, type XXXII

increased during the height of the disease and then gradually became smaller as the process abated Levy¹⁷ observed similar changes in the cardiac shadow

16 Jung, T and Van Allen, C A Method of Recording Respiratory Movements on a Single Roentgenogram, *Nat M J China* **17** 195, 1931

17 Levy, R L The Size of the Heart in Pneumonia A Teleroentgenographic Study, with Observations on the Effect of Digitalis Therapy, *Arch Int Med* **32** 359 (Sept) 1923

The changes in the arterial blood were typical of lobar pneumonia (Stadie,¹⁸ Barach and Woodwell,¹⁹ Meakins and Davies²⁰ and others) The oxygen saturation was below normal in all but one patient (C M) The oxygen capacity was normal There was a moderate reduction in the carbon dioxide content of the arterial blood (a range of from 35 to 44 volumes per cent) When the value for the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ was more than 45 per cent, a certain degree of anoxemia was always present

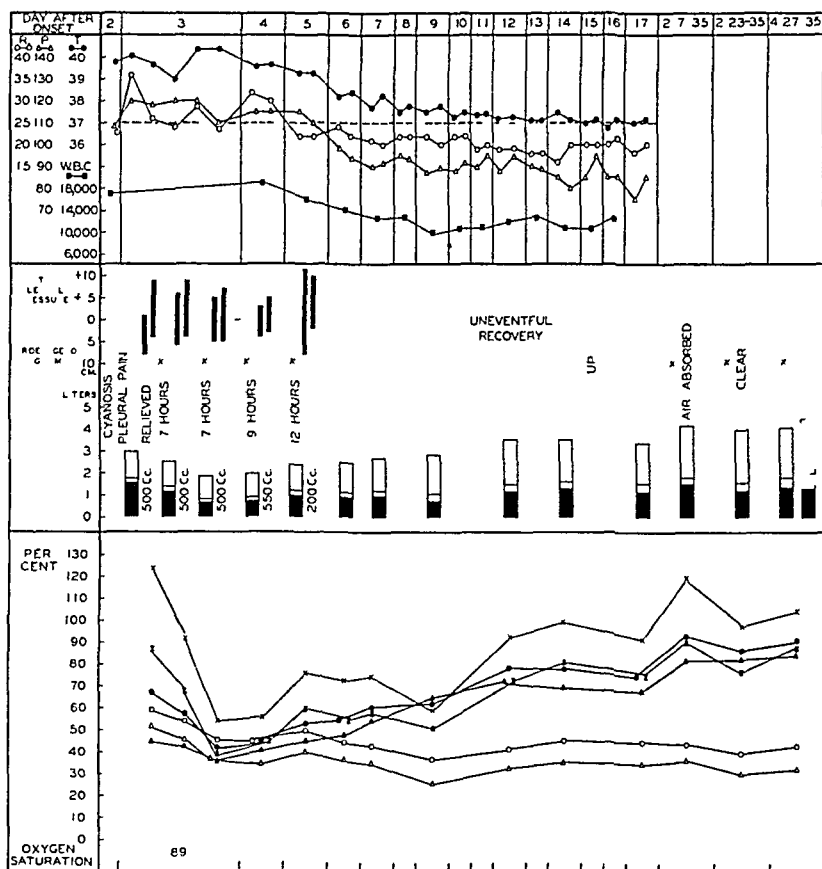


Fig 9—This patient, M L, a woman aged 46, was admitted to the hospital on Jan 8, 1935, and was discharged on January 24. The lower lobe of the right lung was the site of pneumonia due to pneumococci of group 4, type XXXII.

Determinations of the Pulmonary Capacity of Patients with Lobar Pneumonia Treated by Collapse Therapy (Clinical Observations)—Most observers² have agreed that artificial pneumothorax in lobar

18 Stadie, W C. The Oxygen of the Arterial and Venous Blood in Pneumonia and Its Relation to Cyanosis, *J Exper Med* **30** 215, 1919.

19 Barach, A L, and Woodwell, M N. Studies in Oxygen Therapy. II. In Pneumonia and Its Complications, *Arch Int Med* **28** 394 (Oct) 1921.

20 Meakins, J C, and Davies, H W. Respiratory Function in Disease, London, Oliver & Boyd, 1925.

pneumonia is effective only when treatment is instituted early and when the affected lung is quickly and completely compressed. All of our patients were treated early in the course of the disease (on or before the fourth day), but complete collapse or nearly complete collapse was effected in only two (E L and M L) and moderate collapse in one (C M). Total collapse in the other cases was not obtained for several reasons: (1) pleural adhesions were present (T M), (2) either the quantity of air injected was too small or the air was not injected fast enough (A D and I G) or (3) the process spread to the contralateral lung (W H). Usually at each treatment sufficient air was given to establish a positive expiratory pressure with a mean

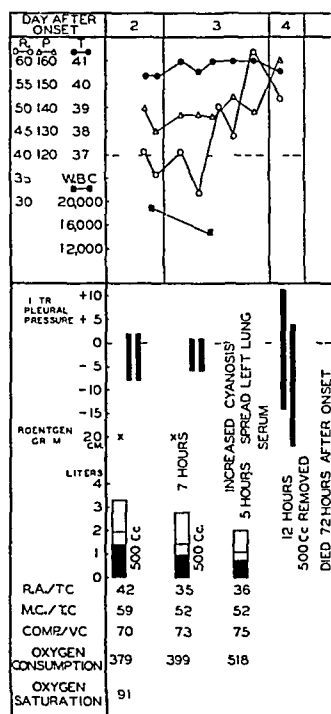


Fig 10—This patient, W H, a man aged 21, was admitted to the hospital on March 11, 1935, and died on March 13. The upper lobe of the right lung was the site of pneumonia due to type I pneumococci.

intrapleural pressure in the neighborhood of 0 mm of water or slightly positive. The total amount of air injected ranged from 350 cc (I G) to 2,250 cc (M L). The clinical results were not striking. Pleural pain when present was relieved in all cases (E L, I G and M L). Two patients (E L and I G) volunteered the remark that they "felt better after the air" was given. The injection of air caused no noticeable change in the pulse or respiratory rates except in one case (T M), in which respiratory distress developed during the second treatment. After 300 cc was removed the distress was relieved. Obvi-

ously, because of the small series of cases, one is not justified in drawing any conclusions concerning the production of a crisis by artificial pneumothorax. Only two complications were encountered, a sterile pleural effusion (I G) and acute respiratory distress (T M). One of the seven patients (W H) treated by collapse therapy died (seventy-two hours after the onset of the disease). At the time treatment was instituted the patient showed physical and roentgenographic evidence of consolidation of the upper lobe of the right lung. Twenty-four hours before death occurred a roentgenogram showed that the left lung was clear. Clinically there was a rapid spread to the opposite side after this, and at autopsy there was early involvement of the entire left lung.

Details of the alterations in the pulmonary capacity are given in figures 4 to 10. After the first injection of air the absolute values for all the components were rapidly and proportionally reduced, and subsequent insufflations caused a less marked diminution. The various capacities expressed in percentages of the predicted values were almost identical after several injections. However, the reduction in the amount of residual air was slightly less than that of the other volumes. There appeared to be some relation between the amount of air given and the degree of diminution in the various capacities. As a rule the decrement of the capacities amounted to a little more than 50 per cent of the predicted values (from 40 to 50 per cent in E L, C M, I G and M L and from 50 to 60 per cent in A D). In one case (T M) the injection of 800 cc of air over a period of twenty-four hours caused no reduction in the volumes.

Interestingly enough, during the establishment of pneumothorax the ratios $\frac{\text{residual air}}{\text{total capacity}} \times 100$ and $\frac{\text{midcapacity}}{\text{total capacity}} \times 100$ were decreased in all cases but one (T M), indicating a more normal relationship of the volume of residual air, the midcapacity and the vital and total capacities.

After the crisis the values for all the different capacities gradually returned to normal. However, the restoration was more rapid in patients without pneumothorax (W A and E G) than in those treated by this procedure. In two patients (E L and M L) the vital and total capacities did not reach their predicted values, even four or six months after the onset of the disease. This discrepancy was due to the formula applied for the prediction. The formula used in these calculations was based on the values obtained for normal women between the ages of 18 and 30 years. Measurements recently made in this clinic for normal women in older age groups indicate that this formula does not apply to older women.

ROENTGENOGRAPHIC MEASUREMENTS

Results of the various measurements are presented in the accompanying table. The height of the pulmonary field on the affected side

and the area of the pulmonary field were larger during maximum collapse than before the establishment or after the disappearance of the pneumothorax (see cases E L and M L, in which the affected lung was almost completely compressed) The measurements in the other cases showed no consistent changes Establishment of pneumothorax in patients with lobar pneumonia had no effect on the degree of dilatation of the heart

COMMENT

Pulmonary Capacity in Patients with Unilateral Pneumothorax — The total and vital capacities and the midcapacity are proportionally reduced in patients with unilateral pneumothorax of several months' duration It has been shown that the decrease in residual air is not proportional to that of the other capacities, resulting in a high value for the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ If the determinations are made shortly after a refill is given, the diminution in this capacity is more marked (J K) than when it is measured several days later (C J and D F). Furthermore, our results show that for pneumothoraces of similar volumes the reduction in the amount of residual air was greater when the affected lung was rapidly collapsed (E L and M L) than when it was more slowly compressed (C J and D F) In other words, some time after the injection of air there occurs a gradual increase in the volume of the residual air This increment is probably due to an increase in the volume of the contralateral lung, usually referred to as "compensatory emphysema" Anthony and Heine^{9a,11} observed that the volume of the contralateral lung increases after the establishment of unilateral pneumothorax

The pathogenesis of this type of emphysema is somewhat different from that of the obstructive type The conditions (such as pneumonia, congestive heart failure, anoxemia, pulmonary fibrosis and pulmonary atelectasis) in which "compensatory emphysema" appears are not usually associated with bronchial obstruction Prinzmetal²¹ said that he believed this is due to pulmonary distention He has shown in acute experiments on animals that in conditions in which there are an increased carbon dioxide and a decreased oxygen tension in the inspired air the intrapleural pressure is more negative and the size of the chest increases When he exposed animals to low oxygen tension over a period of weeks, he found that the alveoli of the lungs were greatly dilated Other investigators found similar changes but with the additional findings of marked congestion of the capillaries (Hurtado²²

21 Prinzmetal, M The Relation of Inspiratory Distention of the Lungs to Emphysema, *J Allergy* 5 493, 1934

22 Hurtado, A Respiratory Adaptation of the Indian Natives of the Peruvian Andes *Studies at High Altitudes, Am J Anthrop* 17 137, 1932

and Huitado and others²³) and a decrease in the distensibility of the lungs (Christie and Meakins²⁴) In many of these conditions, especially congestive heart failure and compression of one lung, in which "compensatory emphysema" develops the circulatory rather than the respiratory factors play the major rôle Von Basch²⁵ on the basis of physical experiments and Christie and Meakins²⁴ on the basis of in vivo observations have shown that the compensatory emphysema associated with cardiac disease is due to circulatory adjustments More recently McIntosh²⁶ pointed out that after thoracoplasty there is increased congestion of the contralateral lung, accompanied with an increase in the volume of the residual air Although the mechanism involved in the production of this type of emphysema has not been determined, we believe, from the information available, that the important etiologic factor is circulatory rather than respiratory However, if either of these mechanisms continues for any considerable period, a loss of pulmonary elasticity, emphysema and a decreased negative intrapleural pressure result If this process is initiated by the respiratory mechanism, one may expect to find a stimulus for increased inspiratory muscular activity, leading to pulmonary distention and hyperventilation of the whole lung or portions of it A little later, or even in the absence of pulmonary distention, there occurs congestion of the capillaries, with decreased distensibility of the lungs, accompanied with a less negative intrapleural pressure The engorgement of the alveolar capillaries and the increased rigidity of the lungs will increase the number and size of the alveolar air spaces, thus tending to increase the amount of residual air and decrease the vital capacity

The relative increase in the amount of residual air in unilateral pneumothorax of some months' duration is in all probability due to such a process It has been generally agreed by most recent investigators (Coryllos and Birnbaum²⁷ gave a review of the literature) that the circulation in the collapsed lung is progressively impaired Since the output of the heart remains unaltered or slightly decreased in some

23 Hurtado, A , Kaltreider, N L , and McCann, W S Respiratory Adaptation to Anoxemia, *Am J Physiol* **109** 626, 1934

24 Christie, R V, and Meakins, J C The Intrapleural Pressure in Congestive Heart Failure and Its Clinical Significance, *J Clin Investigation* **13** 323, 1934

25 von Basch, cited by Lundsgaard, C Determination and Interpretation of Changes in Lung Volumes in Certain Heart Lesions, *J A M A* **80** 163 (Jan 20) 1923

26 McIntosh, C A Respiratory Physiology in Thoracic Surgery, *Ann Surg* **102** 961, 1935

27 Coryllos, P N, and Birnbaum, G L The Circulation in the Compressed Atelectatic and Pneumonic Lung, *Arch Surg* **19** 1346 (Dec) 1929

cases (Nylín,²⁸ Bluhm²⁹ and Cournand, Bryan and Richards³⁰) the volume of the blood and the blood flow must be greater in the uncollapsed lung, resulting in engorgement of the capillaries, which increases the rigidity of the lung and the alveolar air spaces, thus preventing collapse and increasing the volume of residual air. The ventilation (at rest) is the same after pneumothorax as before. Hence the ventilation of the uncollapsed lung must be doubled, thus ensuring a more uniform distribution of air throughout the lung (Meakins and Davies²⁰). This improvement in alveolar ventilation by hyperventilation, however, will be curtailed to some extent by the impairment in pulmonary elasticity and distensibility (Christie and Meakins²⁴).

Alterations in the Pulmonary Capacity in Patients with Lobal Pneumonia—The observations presented indicate that the total and vital capacities are markedly reduced, while the amount of residual air may be slightly decreased or actually higher than the predicted values. The midcapacity is moderately reduced. The variability in the volume of the residual air in this acute infection is not surprising when one considers the numerous factors involved. Atelectasis, bronchial occlusion with obliteration of the alveoli, will tend to reduce the midcapacity and the amount of residual air. On the other hand, there are certain factors, such as pleuritic pain and general muscular weakness, that will prevent the thoracic cage and diaphragm from approaching their normal position at maximum expiration. Consequently, there will be a tendency for the volume of residual air to be increased. Although the process is unilateral, the opposite side cannot act wholly independently, so that even the volume of the healthy lung will be larger at the maximum expiratory position than normally. In three cases (W A, C M and I G) in which we were able to obtain roentgenograms at maximum expiration both before and after the crisis, the area of the pulmonary fields was significantly greater during the height of the disease than during convalescence. In addition to these factors, changes in the parenchyma of the lung itself will influence the volume of the lungs at the midcapacity and maximum expiratory levels. Van Allen and Wu³¹ have shown in experimental pneumonia that there is an increase in the elastic tension of the inflamed lungs. Our preliminary findings in

28 Nylín, G. Untersuchungen über das Minutenvolumen des Herzens in 2 Fällen mit einseitigem künstlichem Pneumothorax, Beitr z Klin d Tuberk **83** 470, 1933

29 Bluhm, I L. Working Test as Clinical Method for Determining the Function of the Lungs, Acta med Scandinav, supp 65, 1935, p 1

30 Cournand, A, Bryan, N A, and Richards, D W, Jr. Cardiac Output in Relation to Unilateral Pneumothorax in Man, J Clin Investigation **14** 181, 1935

31 Van Allen, C M, and Wu, C. Increased Elastic Tension of the Lung in Experimental Pneumonia, J Clin Investigation **11** 589, 1932

several cases of lobar pneumonia support their observations. These alterations, along with congestion of the capillaries in adjacent parts of the consolidated areas and anoxemia, will lead to "compensatory emphysema." All of these factors will likewise influence the other components of the total capacity.

The Respiratory Function in Cases of Lobar Pneumonia in Which Artificial Pneumothorax Was Given—It has recently been shown that abnormally high values for the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ are associated with defective alveolar ventilation.³² The increment in this ratio in patients with lobar pneumonia is an indication that there are underlying factors in the respiratory system which tend to interfere with proper pulmonary ventilation. Thus when pneumothorax is induced in a patient with this disease the affected lung, which is responsible for the derangement of the respiratory function, is compressed, and its effects are greatly minimized. If the lung is completely collapsed and the mean intrapleural pressure is kept positive, ventilation in the affected lung will be negligible, and breathing will be accomplished in a fairly normal manner by the contralateral lung, in spite of a greatly reduced pulmonary capacity. The present work has shown that the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$, which may be taken as an index of pulmonary efficiency, approaches a more normal value after the institution of collapse. Furthermore, it has been shown by others (Means and Balboni³³) that the only difference between a normal subject and a subject with a collapsed lung is that the latter when called on to increase the ventilation reaches his limit sooner than the former. The pulmonary reserve is great, and even though the components of the total capacity are reduced by more than half, the uncollapsed lung (at rest) is able to meet a threefold to fivefold increase in metabolism. If circulation and ventilation are parallel functions,²⁷ after the compression of the affected lung the major portion of the blood will be shunted from it to the aerated lung, thereby increasing the saturation of the arterial blood and conceivably reducing the absorption of toxins.

Little is as yet known of the rapidity with which these respiratory and circulatory adjustments in unilateral pneumothorax are made, but on the basis of available information concerning similar conditions, one is inclined to believe that the process, at least at first, is rapid. In

32 Hurtado, A., Kaltreider, N. L., and McCann, W. S. Studies of Total Pulmonary Capacity and Its Subdivisions. IX. Relationship to the Oxygen Saturation and Carbon Dioxide Content of the Arterial Blood, *J. Clin. Investigation* **14** 94, 1935.

33 Means, J. H., and Balboni, G. M. The Various Factors of Respiration in Persons with Pneumothorax, *J. Exper. Med.* **24** 671, 1916.

experiments on animals Andrus³⁴ found that the blood content of the collapsed lung fell from 100 to 60 per cent during the first half hour. Prinzmetal²¹ has shown that changes in intrapleural pressure and an increase in the capacity of the thoracic cage occurred several minutes after animals were exposed to high carbon dioxide and low oxygen tensions. Furthermore, in three normal subjects²³ it was found that the volume of residual air increased from 30 to 60 per cent after exposure to a barometric pressure of 419 mm of mercury for sixty minutes. Likewise, there was marked dilatation of the capillaries and alveolar air spaces in the lungs of guinea-pigs exposed to the same pressure for two hours. These findings indicate that the circulatory and respiratory adjustments are in process soon after the etiologic factors are initiated.

From the experimental evidence available in the literature it is questionable whether there is an immediate increase in the oxygen content of the arterial blood after pneumothorax is rapidly induced. However, when one lung was collapsed slowly, Meakins and Davies²⁰ found that the arterial blood remained saturated throughout the course and when anoxemia was present prior to collapse therapy it was alleviated by it. Unfortunately thus far we have not had an opportunity to secure arterial blood before and after complete collapse in lobar pneumonia. A conclusion on this point awaits further investigation.

In the light of the foregoing considerations, when collapse therapy is given to a patient with lobar pneumonia he should obtain relief from the following symptoms: (1) pleural pain, (2) respiratory distress and (3) the long list of symptoms due to anoxemia. In numerous papers²² dealing with artificial pneumothorax in the treatment of lobar pneumonia, most authors agree that these symptoms are ameliorated.

The readjustments after the induction of unilateral pneumothorax in lobar pneumonia are complicated because other factors besides respiration exert an influence on the lungs and lesser circulation. Until more clinical and investigative information on these cardiovascular and respiratory factors is available, one is not justified in drawing definite conclusions as to the effect on the cardiorespiratory system or the therapeutic value of the procedure. However, the information at hand suggests that artificial pneumothorax in cases of lobar pneumonia is a rational procedure from the point of view of respiratory function.

34 Andrus, W. deW. Observations on the Cardiorespiratory Physiology Following the Collapse of One Lung by Bronchial Ligation, *Arch Surg* **10** 506 (Jan.) 1925.

35 Klein, T., and Tuck, V. L. Artificial Pneumothorax in the Treatment of Lobar Pneumonia, *Am Rev Tuberc* **32** 511, 1935. Leopold and Lieberman²⁴ Blake, Howard and Hull²⁵

SUMMARY AND CONCLUSIONS

Determinations of the total pulmonary capacity and its components and roentgenographic measurements of the expansion and size of the chest have been made for three patients with pulmonary tuberculosis who were given unilateral pneumothorax, for two patients with lobar pneumonia and for seven patients with lobar pneumonia during the induction of artificial pneumothorax. The gaseous content of the arterial blood was determined in eight of these cases. The results obtained led to the following conclusions:

The total and vital capacities and the midcapacity are proportionally reduced in a patient with unilateral pneumothorax of several months' duration. The volume of residual air is not diminished in proportion to the other capacities, resulting in an increase in the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$.

The effect of posture on the pulmonary capacity of a patient with unilateral pneumothorax is similar to that found in normal subjects.

In a patient with pulmonary tuberculosis with unilateral pneumothorax the excursion of the diaphragm and the movement of the ribs are greatly reduced on the affected side.

Early in the course of lobar pneumonia the total and vital capacities are markedly reduced, while the volume of residual air may be only slightly decreased or actually higher than the predicted volume. The midcapacity is moderately reduced. As the disease progresses the absolute values are further diminished. Beginning several days after the crisis all the volumes gradually return to the predicted levels.

The ability to expand the chest is diminished during the early stages of lobar pneumonia, especially on the affected side. The size of the heart increases both in area and in transverse diameter during the febrile period and diminishes during convalescence.

The oxygen saturation and the carbon dioxide content of the arterial blood are reduced during the early stages of lobar pneumonia.

During the induction of artificial pneumothorax in cases of lobar pneumonia the total capacity and all its subdivisions (expressed as percentages of the predicted values) are proportionally reduced, resulting in a more normal relationship between the volume of residual air and the total capacity.

The height of the pulmonary field, measured on a roentgenogram, on the side of the pneumothorax and the area of the pulmonary field at maximum inspiration are increased during the period of maximum collapse.

The factors responsible for the alterations in the total pulmonary capacity and its subdivisions in lobar pneumonia and collapse therapy are discussed.

RENAL INSUFFICIENCY FROM BLOOD TRANSFUSION

I RELATION TO URINARY ACIDITY

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From 1667, when the first blood transfusion was given to man by Jean Baptiste Denys,¹ until the discovery of hemagglutination by Landsteiner² in 1901 and the classification of blood groups by Jansky³ (1907) and Moss⁴ (1910), hemoglobinuria was accepted as a common accompaniment of the injection of blood intravenously. In many of the patients who showed hemoglobin in the urine renal insufficiency developed, and death followed. Since testing the donor's and the recipient's blood for agglutination has become common, the incidence of severe complications from blood transfusions has, fortunately, greatly diminished. Hesse and Filatov^{18a} reported a mortality of 13 per cent from 750 transfusions in Leningrad. They estimated that in general the mortality in various clinics was between 0.5 and 1.5 per cent. Tiber⁵ (1930) reported 2 deaths from 1,467 transfusions (0.013 per cent) at Bellevue Hospital. Witts⁶ described 3 deaths in 3,430 transfusions in Great Britain. Wildegans⁷ placed the mortality from blood transfusions between 0.1 and 0.2 per cent.

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1 Denys, J. B., quoted by Keynes, G. *Blood Transfusion*, New York, Oxford University Press, 1922

2 Landsteiner, K. *Ueber Agglutinationserscheinungen normalen menschlichen Blutes*, Wien klin Wchnschr **14** 1132, 1901

3 Jansky, J. *Haematologische Studien bei Psychotikern*, Klin Sborn **8** 85, 1907

4 Moss, W. L. *Studies on Isoagglutinins and Isohemolysins*, Bull Johns Hopkins Hosp **21** 63, 1910

5 Tiber, A. M. *Observations on Blood Grouping and Blood Transfusion*, Ann Surg **91** 481, 1930

6 Witts, L. J. *Note on Blood Transfusion*, Lancet **1** 1297, 1929

7 Wildegans, H. *Die Bluttransfusion*, Berlin, Julius Springer, 1933, p. 131

Many of the deaths following blood transfusion are apparently due to renal insufficiency. There are many excellent descriptions of this syndrome in the literature. Commonly the transfusion is accompanied, or soon followed, by pain in the lumbar region or thighs, a feeling of constriction in the chest, chills and fever. Shock often occurs. Icterus may develop within a few hours. Hemoglobinuria is usually present. Partial or complete suppression of the urinary excretion may ensue with consequent retention of nitrogen. When the renal function is impaired the patient usually dies in coma from four to fifteen days after the transfusion, although a few patients recover spontaneously. The recipient's serum has been proved to agglutinate the donor's cells in most instances, but no such incompatibility has been proved in some cases. Pathologic studies show that the principal organ affected is the kidney. There is interstitial cellular infiltration. The glomeruli are normal or dilated. The tubular epithelium shows various degrees of degeneration, while the lumens contain leukocytes, debris and masses of brownish pigment. Lindau⁸ and Bordley⁹ have presented excellent reviews of the recent literature. Lindau called attention to the similarity between the clinical and the pathologic picture of transfusion anuria and the anuric episodes occurring in blackwater fever. The relationship had previously been noted by Baker and Dodds¹⁰. Dudgeon¹¹ observed various degrees of renal damage in patients dying of blackwater fever, but Whipple¹² could not attribute any injury to hemoglobinuria per se in the patients he studied.

Our interest in this subject was stimulated by the occurrence in the University Hospital of two fatal cases of renal insufficiency following blood transfusion. These have been reported elsewhere¹³. As both our clinical experience and a review of the literature pointed to no promising therapeutic procedures in this condition, the problem was attacked experimentally.

As early as 1875 Ponfik¹⁴ produced a somewhat similar clinical and pathologic picture in dogs by the injection of heterogenous blood

8 Lindau, A. Reaktionen nach Bluttransfusion. Eine atologische und pathologisch-anatomische Studie, *Acta path et microbiol Scandinav* **5** 383, 1928.

9 Bordley, J. Reactions Following Transfusion of Blood, with Urinary Suppression and Uremia, *Arch Int Med* **47** 288 (Feb) 1931.

10 Baker, S. L., and Dodds, E. C. Obstruction of the Renal Tubules During the Excretion of Hemoglobin, *Brit J Exper Path* **6** 247, 1925.

11 Dudgeon, L. S. Blackwater Fever, *J Hyg* **19** 208, 1921.

12 Whipple, G. H. Pathology of Blackwater Fever, *Am J Trop Med* **7** 1, 1927.

13 DeGowin, E. L., and Baldrige, C. W. Fatal Anuria Following Blood Transfusions. Inadequacy of Present Tests for Compatibility, *Am J M Sc* **188** 555, 1934.

14 Ponfik. Experimentelle Beitrage zur Lehre von der Transfusion, *Virchows Arch f patl. Anat* **62** 273, 1875.

Levy¹⁵ supplemented these observations by producing experimental hemoglobinuria in rabbits. He concluded that the excretion of hemoglobin produced the renal lesions. In 1911 Yorke and Nauss¹⁶ reported that anuria and subsequent death could be produced by the intravenous injection of homogenous hemoglobin into rabbits fed on dry diets. This phenomenon did not occur when the animals were eating green food. The authors explained these results by postulating that the filtration pressure of the glomeruli was lowered by the low intake of fluid. Baker and Dodds,¹⁰ however, challenged this explanation and produced experiments to show that the real difference lay in the fact that the rabbits in which renal insufficiency developed had acid urine, while those with alkaline urine were protected. They reported also in vitro experiments to show that solutions of hemoglobin were precipitated in acid solutions as acid hematin and that this reaction was augmented by the presence of more than 1 per cent sodium chloride. These authors considered that the pathologic and chemical picture could be entirely explained by the precipitation of hemoglobin in the tubular lumens in an acid solution with a high concentration of electrolyte, thus producing intrarenal obstruction.

Recent evidence has been introduced to show that renal ischemia may be an important factor in this problem. Mason and Mann¹⁷ reported a transient decrease in the volume of the dog's kidney due to intravenous injections of hemoglobin. The glomeruli of the dog's kidney were observed to constrict under similar conditions. From the Scientific Institute for Blood Transfusion in Leningrad have come the reports of a series of studies by Hesse and his co-workers¹⁸. They have observed a

15 Levy, L. Untersuchungen über die Nierenveränderungen bei experimenteller Hämoglobinurie, *Deutsches Arch f klin Med* **81** 359, 1904.

16 Yorke, W., and Nauss, R. W. The Mechanism of the Production of Suppression of Urine in Blackwater Fever, *Ann Trop Med* **5** 287, 1911.

17 Mason, J. B., and Mann, B. F. Effect of Hemoglobin on the Volume of Kidney, *Am J Physiol* **98** 181, 1931.

18 (a) Hesse, E., and Filatov, A. Experimentelle Untersuchungen über das Wesen des hämolytischen Schocks bei der Bluttransfusion und die therapeutische Beeinflussung desselben. I Die Nierenfunktionsstörungen im akuten Experiment, *Ztschr f d ges exper Med* **86** 211, 1933. (b) Petroff, J., Filatov, A., Bogomolova, L., and Stroiikova, X. I Die Pathogenese der Veränderungen des Herzens und der Gefässe, *Arch f klin Chir* **181** 209, 1934. (c) Wesselkin, P., Lindenbaum, J., and Kartashevskiy, N. G. II Die Rolle des Zentralnervensystems in der Pathogenese der Gefässstörungen beim hämolytischen Schock, *ibid* **181** 227, 1934. (d) Iljin, W. III Experimentelle Beobachtungen der Nierentätigkeit nach Einführung von heterogenem und autohämolyisiertem Blut, *ibid* **181** 240, 1934. (e) Filatov, A. Klinische und experimentelle Beiträge zur Reinfusion des in die Körperhöhlen ergossenen Blutes, *ibid* **151** 184, 1928. (f) Hesse, E., and Filatov, A. Neue praktische Ausblicke auf die Möglichkeit der Behandlung des hämolytischen Schocks bei der Bluttransfusion im Lichte experimenteller Forschung, *Zentralbl f Chir* **59** 2674, 1932.

transient diminution in the renal volume and a fall in the systemic blood pressure following the injection into dogs of hemolyzed homogenous blood or whole human blood. The changes were more marked with the heterogenous blood and less marked with citrated blood which had been preserved for ten days. It was shown that the primary mechanism was the constricting action of the hemoglobin on the renal vessels themselves. Transfusions of compatible blood relaxed the spasm of the renal vessels and restored the function of the kidney. It was frequently possible to kill a dog with a single transfusion of human blood, but rarely did canine blood prove fatal. The dogs died two or three days after a transfusion, with mild retention of nitrogen and suppression of urine. The pathologic studies have not yet been published. The Russian workers have abandoned the theory that renal insufficiency is due to obstruction by precipitated hemoglobin. They have stated as their belief that the impairment of the renal function and the consequent pathologic changes can all be explained by spasm of the renal arteries and the resulting ischemia.

The injection of solutions of homogenous hemoglobin intravenously has been generally considered to be an innocuous procedure (Bayliss¹⁹). Havill, Lichty, Taylor and Whipple²⁰ demonstrated that hemoglobin is a threshold substance for the kidney of the dog and that it is probably excreted through the glomeruli, as the threshold is not changed when the tubules have been poisoned with mercury bichloride. Kerridge and Bayliss,²¹ on the basis of perfusion experiments, concluded that proteins with a molecular weight greater than 68,000 do not filter through the glomeruli, while those of smaller size do. Hemoglobin, with a molecular weight of approximately 68,000, is a borderline substance and at times does filter through the glomerular membrane. Drabkin, Wideman and Landow²² have recently shown by spectrophotometric analyses that when hemoglobin is injected intravenously into a dog, it rapidly disappears from the blood serum but that only about 10 per cent appears in the urine. It is excreted as hemoglobin, but on standing in contact with urine it is rapidly changed to methemoglobin.

19 Bayliss, W. M. Is Hemolyzed Blood Toxic? *Brit J Exper Path* **1** 1, 1920

20 Havill, W. H., Lichty, J. A., Jr., Taylor, G. B., and Whipple, G. H. II Renal Threshold for Hemoglobin in Dogs Uninfluenced by Mercury Poisoning, *J Exper Med* **55** 617, 1932

21 Kerridge, P. M. T., and Bayliss, L. E. Physiology of Proteinuria, *Lancet* **2** 785, 1932. Bayliss, L. E., Kerridge, P. M. T., and Russell, D. S. Excretion of Protein by Mammalian Kidney, *J Physiol* **77** 386, 1933

22 Drabkin, D. L., Wideman, A. H., and Landow, H. The Fate of Hemoglobin Injected into the Blood Stream, *J Biol Chem* **109** 227, 1935

METHODS

All the dogs used in our studies were kept in metabolism cages during the periods of observation so that voided urine could be collected. Catheterization was not performed, as we wished to avoid infection of the urinary tract as far as possible. Observations were usually made on twenty-four hour specimens to which toluene had been added. The volume, color and specific gravity were noted. Chemical tests were made for the presence of albumin, dextrose and hemoglobin. The centrifugated sediment was examined for casts, blood corpuscles and clumps of pigment. In our first experiments the reaction of the urine was tested with litmus paper. This proved not delicate enough, and later the approximate p_H was determined by a series of indicators, such as phenol red, bromthymol blue and bromcresol purple.

Blood was obtained from dogs which had been used for classes in surgical technic and had been under ether anesthesia for two hours. Blood was collected from the femoral arteries by means of paraffined cannulas and then defibrinated by being shaken in large Erlenmeyer flasks with bent wire paper clips. The defibrinated blood from several dogs was pooled and then centrifugated for forty-five minutes at 2,500 revolutions per minute, and the serum and the layer of leukocytes were drawn off with a pipet. The red blood corpuscles were not washed, as experiments reported in the literature of the innocuousness of serum did not seem to warrant the great amount of work entailed. The corpuscles were stored in a refrigerator usually for one day, occasionally longer, and then used. The cells were hemolyzed by being mixed with distilled water in the proportion of three parts of cells to four parts of water by volume. The solution of hemoglobin was injected into the jugular vein by gravity, the velocity being controlled so that it rarely exceeded 20 cc per minute. The dogs were not anesthetized during the transfusion and, with few exceptions, seemed to suffer no inconvenience at the time. Specimens of blood for chemical analysis were obtained immediately preceding transfusion and at twenty-four-hour intervals thereafter until the death of the dog or until normal values for urea were attained.

Transfusions were given to each dog at intervals of from one week to several months, never being given more frequently. Care was taken to administer transfusions of the same pooled blood to as many dogs on alkaline diets as on acid diets. This served as a control on the toxicity of the blood from incidental causes. Post-mortem examinations were performed as soon after death as possible, and routine histologic examinations were made of the kidneys, adrenal glands, liver, mesenteric lymph nodes, spleen, cardiac muscle, lungs and bone marrow from the femur.

EXPERIMENTAL OBSERVATIONS

So far, studies have been made on a series of twenty-eight dogs over a period of more than two years. Of this number, seven died of renal insufficiency following a transfusion, two were killed when recovering from the same syndrome, three survived an episode of uremia, two died during a transfusion (apparently from speed shock), six died of an intercurrent infection, two were killed when in good health after many transfusions and one was discarded because it was ugly. Five are still living, the data being too insufficient to report in detail at this time.

Over one hundred transfusions of dog hemoglobin have been given. Most of the dogs showed no symptoms during the transfusion if the solution was administered slowly. The hemoglobin appeared in the urine

almost immediately in quantities sufficient to color it. The urine continued to be reddish for one or two days, and chemical tests showed the presence of hemoglobin for two more days. When there was no significant retention of nitrogen the dogs appeared well. A small amount of albumin occurred in the urine along with gross hemoglobinuria. Microscopic examination of the urinary sediment revealed various-sized masses of reddish brown pigment in the form of conglutinated globules. There were no casts or red blood corpuscles.

If retention of nitrogen occurred after a transfusion, the animal was less active than normal and soon began to vomit. It refused food but drank a large quantity of water, which was quickly regurgitated and seemed to serve as gastric lavage. If it did not recover, the course was clinically progressive, and the urea and creatinine values of the blood rose daily. A day before death the dog was so weak it could not stand. The muscles became somewhat rigid, and there was occasional twitching. Generalized convulsions were observed. A few hours before death the dog became comatose. Dogs died with this syndrome from four to ten days after a transfusion. The final values for the urea nitrogen of the blood varied from 119 to 362.6 mg per hundred cubic centimeters and for creatinine from 4.6 to 15 mg. Occasionally some degree of alkalosis developed before an animal died, as determined by the carbon dioxide capacity and the chloride values of the plasma. When retention of nitrogen developed after a transfusion, the urinary sediment contained numbers of large casts composed of dense masses of brownish pigment. The maximum number was usually seen on the second day after the transfusion and were a reliable index as to whether retention of nitrogen was present in a given animal. These casts have been described as seen in rabbits and were photographed by Baker and Dodds¹⁰.

After a seemingly innocuous transfusion or after recovery from an episode of retention of nitrogen the urine is entirely normal, as judged by the specific gravity and the absence of albumin, dextrose, casts, hemoglobin pigments and erythrocytes.

Alkaline Diets—Dogs seem to live normally and grow fat on vegetable scraps from the hospital kitchens. The entire dog colony of the medical college has been kept on this diet for years. Dogs 3, 4, 12 and 13 were kept on this diet and received from eight to fourteen transfusions of solution of dog hemoglobin without any deaths. Their protocols are summarized in table 1. Usually no significant rise in the urea content of the blood was noted. In dog 4, however, there was an appreciable retention of nitrogen after several of the earlier transfusions. We are uncertain as to the explanation for this, but it is possible that the dog was not eating and that the urine was slightly acid. The speci-

mens of urine were being tested for acidity with litmus paper at the time, a method that was later found to be inadequate. The protocol of dog 12, as set forth in table 2, is interesting. This animal was fed an alkaline diet over a period of eight months, but on several occasions it

TABLE 1—Data for Dogs on Alkaline Diets

Dog	Sex	Weight, Kg	Number of Trans- fusions	Hemoglobin Injected, Cc *	Maximum Blood Values After Transfusion		Comment
					Urea Nitrogen, Mg per 100 Cc	Creatinine, Mg per 100 Cc	
3	♀	90	14	19.0	14.0		All urine alkaline
				27.7	18.2	1.0	
				15.0	16.8	1.0	
				14.0	57.4	3.3	
				16.6	57.4	2.5	
				13.3	39.9	1.5	
				16.6	53.9	1.2	
				6.6	18.2	1.1	
				14.4	15.4	1.0	
				16.6	29.4	1.2	
				16.6			
				16.6	37.1	1.2	
				14.0	21.0	1.2	
				16.6	20.3	1.2	
4	♀	80	9	18.7	88.9	4.4	All urine alkaline
				14.4	113.4	5.0	
				7.5	74.9	5.0	
				15.0	59.5	3.0	
				18.7	50.4	1.2	
				18.7			
				18.7	76.3	3.4	
				15.6	51.1	2.2	
				18.7	60.9	2.7	
12	♀	85	10	15.0	121.0	1.3	Urine acid
				8.0	23.8	1.2	Urine alkaline
				9.4	151.2	5.5	Urine acid
				10.0	26.0	1.0	Urine alkaline
				10.0	21.0	1.0	Urine alkaline
				8.6	26.6	1.0	Urine alkaline
				8.3	22.0		Urine alkaline
				12.0	27.0		Urine alkaline
				3.0	18.9		Urine alkaline
13	♀	160	8	12.0	133.7	4.4	Urine acid, killed Typical nephropathy
				15.0	20.3	1.1	All urine alkaline
				7.2	22.0	1.0	
				9.3	21.0	1.1	
				11.2	7.0	1.0	
				11.2	11.9	1.0	
				11.2	15.4	1.0	
				8.6	35.4	1.3	
				26.0	21.0		
				6.0	20.3	1.0	13 divided doses (daily) Living 3 months later

* The amount of hemoglobin injected is expressed in cubic centimeters of packed erythrocytes per kilogram of body weight before hemolysis

refused to eat and the urine became acid. Transfusions while the urine was alkaline proved innocuous, but when hemoglobin was injected in the presence of acid urine, retention of nitrogen developed. While recovering from one episode of azotemia, the dog was killed and the typical nephropathy associated with death due to renal insufficiency was

observed Dogs 3 and 4 were killed after receiving fourteen and nine transfusions, respectively. No lesions were seen, except depositions of iron-containing pigment in the spleen, liver, lymph nodes and epithelial cells of the convoluted renal tubules.

Acid Diets—Dogs were kept on diets consisting of cooked chopped beef, about $\frac{1}{2}$ pound (225 Gm) per day, with which was mixed about 8 Gm of ammonium chloride. Beef alone often failed to make the urine

TABLE 2—Data for Dog 12 on an Alkaline Diet with Varying Urinary Reaction

Date, 1935	pH of Urine	Blood				Weight 9 kg
		Urea Nitrogen, Mg per 100 Cc	Creatinine, Mg per 100 Cc	Plasma Chlorides, Mg per 100 Cc	Carbon Dioxide Capacity, Vol %	
2/23	6.8	13.3	1.0	675	49.0	Transfusion
2/25		11.9	1.0	625	41.0	
2/27		70.0	1.3	690	39.0	
3/ 2	6.8	121.0	1.3	550	50.0	Transfusion
3/ 7		23.8	1.2	625	62.0	
3/16	6.8	17.5	1.0	665	48.0	Transfusion
3/17		39.9	2.5	625	47.0	
3/18		89.9	3.5	612	48.5	
3/19		86.1	3.8	660	48.0	
3/20		119.0	4.3	640	38.0	
3/21		135.0	4.4	640	37.0	
3/22		151.2	5.5			
3/23		106.4	4.7	700	30.0	
3/24		114.8	4.4	600	38.0	
3/26		86.8	4.4			
3/28		56.0				
4/ 6	7.2	14.0	1.0		45.0	Transfusion
4/ 8		26.0	1.0	615	47.0	
4/13	7.0	12.6	1.0	625		Transfusion
4/15		21.0	1.0			
5/ 4	7.2	12.0	1.0	415	39.0	Transfusion
5/ 6		26.6	1.0	600	32.0	
10/13	7.4	13.0	1.0	452	28.0	Transfusion
10/14		22.0	1.0	419	36.0	
10/19	7.0	16.0	1.0	460	42.0	Transfusion
10/25		26.6	1.0	441	51.0	
11/11	7.8	18.2	1.0		35.2	Transfusion
11/12		18.9	1.1		48.5	
12/ 1	6.0	9.8	1.0	640	52.2	Transfusion
12/ 3		99.4	3.5	581	41.9	
12/ 6		123.9	4.8		37.2	
12/ 8		133.7	4.4	600	40.9	
12/10		117.0	4.6	690	42.8	

persistently acid. The dogs would not eat food which contained much more than 8 Gm of ammonium chloride and occasionally refused this amount for several days at a time. The dogs usually held their weight on this diet and, while there was a tendency for the carbon dioxide capacity to become lower and for the chloride content of the plasma to become higher, this was not constant and remained within the limits of variation of the values for dogs on the alkaline diets.

We were naturally concerned with the effects of the diet itself on the renal function and pathologic picture. Neither albuminuria nor

cylindruria developed as a result of the diet alone. Of twenty-three dogs which had been on this diet for varying lengths of time up to five months, only in dog 8 did glycosuria develop at the end of three months. This disappeared when an alkaline diet was substituted and has not returned, although the acid diet has been resumed. Dog 7 died of speed shock during a transfusion, and although it had been on the diet continuously for four months, no histologic lesions were seen which could be attributed to the diet.

TABLE 3—Data for Dogs on Acid Diets

Dog	Sex	Weight, kg	Number of Trans- fusions	Hemo- globin, Injected, Cc	Maximum Blood Values After Transfusion		Comment*
					Urea Nitrogen, Mg per 100 Cc	Creat- inine, Mg per 100 Cc	
1	♂	9.3	3	5.5 22.2 27.7	26.6 120.4		Died in coma 10 days after trans- fusion, typical nephropathy
2	♂	7.0	2	14.2 35.7	20.3 217.7	5.7	Died in coma 8 days after trans- fusion, typical nephropathy
3	♀	10.0	3	12.5 15.0 12.5	39.9 70.7 217.7	2.4 3.2 4.6	Died in coma 7 days after trans- fusion, typical nephropathy
10	♀	11.0	7	12.3 11.0 9.0 10.0 10.0 10.0 8.4	21.0 30.1 30.1 18.2 17.5 18.9 19.6	0.9 1.7 2.1 1.0 1.0 1.2 1.0	Living 3 months later
11	♀	10.0	2	8.0 11.4	16.8 350.0	1.0 12.5	Died in coma 4 days after trans- fusion, typical nephropathy
20	♀	11.4	1	9.0	119.0	5.3	Killed when recovering 5 days after transfusion, urea nitrogen 95.9 mg, creatinine 3 mg, typical nephropathy
21	♂	10.0	1	10.0	266.0	10.0	Died in coma 5 days after trans- fusion, typical nephropathy
8	♂	12.0	2	10.0	85.4	3.0	Survived
22	♀	11.0	1	9.5	81.9	3.5	Survived
23	♂	8.5	1	10.0	324.1	12.2	Died in coma 7 days after trans- fusion, typical nephropathy
24	♀	9.5	1	9.0	362.6	15.0	Died in coma 6 days after trans- fusion, typical nephropathy
26	♂	9.5	1	10.0	123.9	5.0	Survived

* All the specimens of urine were acid.

† The amount of hemoglobin injected is expressed in cubic centimeters of packed erythrocytes per kilogram of body weight before hemolysis.

Of the twenty-three dogs which received transfusions while on acid diets, seven died of renal insufficiency and one was killed when recovering. All showed the typical nephropathy, to be described. One dog received seven transfusions without effect and died later of intercurrent infection. The protocols of these are summarized in table 3. In dogs 20, 21, 23 and 24 retention of nitrogen developed after the first transfusion. The others died after two, two, three and three transfusions,

respectively Dogs 7 and 19 died of speed shock Dogs 9, 10, 13, 14 15 and 16 died of intercurrent infection Dogs 17 and 18 are still living, the data being insufficient to record at this time The protocol of a typical dog on an acid diet is given in table 4

Changes in Urinary Volume—After transfusion there was generally diuresis during the first twenty-four hours In only two dogs (dogs 11 and 21) was there suppression of urine after a transfusion, and in these cases there was anuria for the four and five days, respectively, elapsing between the transfusion and the death in coma²³ In the other dogs

TABLE 4—Protocol of Dog 5 on Acid Diet

Date, 1934	Volume, Cc	Specific Gravity	Urine			Blood		
			Reaction	Albumin	Hemo globin	Urea Nitrogen, Mg per 100 Cc	Creatinine, Mg per 100 Cc	
5/19	200	1 018	Acid	0	0	12 2	1 0	Transfusion
5/20	700	1 008	Acid	++	++++			
5/21	0					28 0	2 4	
5/22	975	1 015	Alkaline	0	++			
5/23	0							
5/24	300	1 015	Acid	+	+			
5/25	650	1 015	Acid	Trace	Trace	39 9	1 6	Transfusion
5/26	600	1 015	Acid	0	0			
11/17	100		Alkaline	0	0	12 2	1 0	
11/18	700		Alkaline	++	++++			
11/19	500	1 006	Alkaline	+	++++	60 2	3 0	
11/20	400	1 010	Alkaline	+	+++			
11/21	600		Acid	0	+	70 7	3 2	
11/22	0							
11/23	1,000		Acid	0	Trace			
11/25						47 6	1 3	
12/ 3						28 0	1 1	
12/ 8	500	1 010	Acid	0	0	18 9	1 0	Transfusion Vomiting Vomiting Vomiting Vomiting Rigidity Comatose
12/ 9	560		Acid	++	++++	56 0	2 8	
12/10	1,100		Acid	+	+++			
12/11	425†	1 006	Acid	0	++	159 6	5 0	
12/12	550†	1 012	Acid	Trace	++			
12/13	950†	1 008	Neutral	Trace	+	176 0	4 6	
12/14	0							
12/15	900†	1 009	Acid	Trace	Trace	217 7	4 6	
12/16	Died in coma, typical nephropathy							

† The urine contained many casts of hemoglobin pigment

that died of renal insufficiency the volume of urine excreted continued to be fairly high until death occurred The amounts could not be accurately estimated because under the conditions of collection the urine was frequently mixed with vomitus

Renal Vasoconstriction—We made no direct observations of this phenomenon in our material We doubt whether it was an important factor, however, because many of the dogs voided bright red urine

23 It is notable that of the dogs that died of renal insufficiency dog 11 had the most rapid death and high terminal values for the urea and creatinine contents of the blood

containing hemoglobin immediately after the conclusion of a transfusion, and, as has been noted, there usually was diuresis during the first twenty-four hours

Speed Shock—Dogs 7 and 19 died on the table during a transfusion. While the solution of hemoglobin was running into the jugular vein, restlessness developed, with sudden dyspnea and convulsive movements. In dog 7 respiration and the heart beat stopped simultaneously. In dog 19 the heart continued to function for several minutes after respiration had ceased. Autopsy revealed nothing but a rather dilated heart and engorged jugular veins. An examination of the brain and spinal cord was not made, however. In the first case the velocity of the transfusion had been fast. In the second case the rate was 6 cc of solution per minute. During the course of many transfusions it was observed that a velocity of over 20 cc per minute frequently induced dyspnea and transient convulsive movements, which promptly disappeared when the velocity was decreased. Hirshfeld, Hyman and Wanger²⁴ described this syndrome and named it. They showed that it could be produced by the rapid intravenous injection of a number of unrelated substances, such as hypotonic, isotonic and hypertonic solutions, sugars, colloids and gels, suspensions and blood.

Repeated Transfusions—Of the seven dogs that died of renal insufficiency, three died after one transfusion, two after two transfusions and two after three transfusions. There was no chemical evidence of an accumulative effect from previous transfusions. An experiment was set up to test this factor. Dog 13 was given an alkaline diet, and dog 15 was given an acid diet. Each received thirteen small daily injections of the same lot of dog hemoglobin. The dose was 2 cc per kilogram of packed corpuscles hemolyzed with distilled water. These injections caused continuous hemoglobinuria for fifteen days. The urea and the creatinine content of the blood remained normal for both dogs.

Pathologic Examination—A detailed study of the pathologic picture in human beings who died as a result of a blood transfusion and in the dogs which we used will be reported in another paper. In the dogs that died of renal insufficiency the significant lesions were confined to the kidneys. The glomeruli were normal. The lumens of the distal segments of the renal tubules were filled with brownish pigment that was closely packed and, in some places, in crystalline form. The pigment was so arranged as to block the tubules completely. The capillaries were engorged, and there was some interstitial leukocytic

24 Hirshfeld, S. Hyman, H. T., and Wanger, J. J. Influence of Velocity on the Response to Intravenous Injections, *Arch. Int. Med.* **47**: 259 (Feb.) 1931.

infiltration. Some of the tubules were filled with leukocytes also. The tubular epithelium seemed to be little damaged. The lesion appeared to be purely obstructive.

COMMENT

In our experiments the chemical studies of the blood and the pathologic picture of the renal lesions seemed to favor the explanation that renal insufficiency due to blood transfusion can be caused by precipitation of hemoglobin in the renal tubules and the production of insufficiency by obstruction. This is at variance with the theory of Hesse and his co-workers, which attributes the primary cause to vasoconstriction of the kidneys. We wish to point out some apparent differences between the syndrome produced in our dogs and that set forth in Iljin's^{18d} report. In the Russian experiments whole human blood was injected into a series of nine dogs. Five survived and four died. These four all showed anuria and died two days after the transfusion, with relatively slight retention of nitrogen. Those surviving had temporary oliguria. Eight dogs were given a transfusion of their own hemolyzed blood. Seven survived, and one died in three days with an undetermined amount of retention of nitrogen. No mention is made of the type of diet or of the reaction of the urine. A report on the pathologic studies has not yet been published. In many cases the velocity of transfusion was much faster than that which we employed. From their protocols we have calculated that the average velocity of transfusion in the cases of the dogs that died was 357 cc per minute. We were unable to give a solution of hemoglobin as fast as that without causing symptoms of speed shock. So it seems possible that the Russian workers are studying a different syndrome from the one we have here reported.

The fact that several transfusions have been required to produce renal insufficiency in many of our dogs can be given various interpretations. Since four dogs have shown retention of nitrogen, with the typical pathologic picture after a single transfusion, the possibility of anaphylaxis is precluded. Renal lesions due to acidosis or alkalosis per se seem to be ruled out by our chemical studies. We choose to believe that there is still another factor besides urinary acidity which remains to be elucidated and, when controlled, it will enable us to produce the syndrome more consistently.

At the time the present article was being written a paper appeared by Melnick, Burack and Cowgill²⁵ which reported a series of experi-

25 Melnick, D., Burack, E. and Cowgill, G. R. Development of Incompatibilities in Dogs by Repeated Infusions of Red Blood Cells. *Proc. Soc. Exper. Biol. & Med.* **33**: 616 (Jan.) 1936.

ments in which dogs were repeatedly given transfusions of citiated blood from the same canine donors. Apparently very low titers of agglutinins and hemolysins in the recipients were increased after each transfusion, so that the results were clinically significant. We have not had time to study this phenomenon in relation to our work, but it should be pointed out that we used hemolyzed blood entirely, which was always pooled from three or four dogs and distributed among four dogs, and the syndrome produced that was due to renal insufficiency was unlike that ascribed to incompatible dog blood. The authors reported that no pathologic lesions were observed.

SUMMARY

When the urine is alkaline the intravenous injection of a large amount of dog hemoglobin into dogs seems to be innocuous. Under such conditions four dogs received a total of thirty-eight transfusions without harm. In one of the dogs retention of nitrogen developed on three occasions when the transfusion was given while the urine was acid.

When the urine is acid, transfusions of hemoglobin sooner or later produce renal insufficiency. Seven dogs died in coma from four to ten days after the transfusion, with the urea nitrogen values of the blood ranging between 120 and 362.6 mg per hundred cubic centimeters and creatinine values between 4.6 and 15 mg. One dog was killed when recovering, the urea nitrogen content of the blood being 95 mg. Only one dog survived seven transfusions when on an acid diet. This syndrome, clinically and chemically, closely simulates that which develops in human beings with renal insufficiency resulting from hemoglobinuria.

From pathologic studies it appears that the cause of renal insufficiency resulting from hemoglobinuria in dogs is the obstruction of the tubular lumens with masses of pigment derived from hemoglobin.

These studies substantially confirm the experiments performed on rabbits by Baker and Dodds.¹⁰

Assistance was rendered by Dr. C. W. Baldrige before his death in an automobile accident on Nov. 22, 1934. Dr. H. P. Smith, professor of pathology, and Dr. R. B. Gibson, associate professor of biochemistry, gave advice on many matters. The members of the department of surgery made it possible for us to secure large quantities of dog blood.

CHANGING INCIDENCE OF TUBERCULOSIS OF THE TONSILS

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Numerous investigations have dealt with the incidence of tuberculosis in surgically removed tonsils. However, the majority of the earlier reports were based on relatively small series of cases or on selected cases, from which the true incidence of tuberculosis in surgically removed tonsils in all age groups, irrespective of the presence or absence of tuberculosis elsewhere, could not be determined.

Weller¹ was the first to report a series of sufficient length and nonselectivity to answer this question. The tonsils studied comprised the surgical material received as a routine in this laboratory during the years 1906 to 1919. The faucial and/or pharyngeal tonsils of 8,607 patients were studied, and the incidence of tuberculosis for the entire group was found to be 2.35 per cent.

As the literature previous to 1921 was comprehensively reviewed in that paper,¹ it will not be dealt with here. Since 1921 few series of sufficient size to be of value have been reported. Mullin² analyzed 400 tonsils and found the proportion with tuberculous infection to be 4.25 per cent, but it should be noted that in 60 per cent of his cases there was clinical evidence of tuberculosis elsewhere. MacCready and Crowe³ found an incidence of 4.18 per cent in the examination of tonsils of 3,260 children. Howarth⁴ found tubercles in 5 per cent of 100 tonsils of children from 3 to 15 years old. For a series of 200 patients in the same age group Scarff and Whitby⁵ reported an incidence of 2 per cent.

From the Department of Pathology, the University of Michigan

1 Weller, Carl V. The Incidence and Histopathology of Tuberculosis of the Tonsils, Based on Eight Thousand Six Hundred Tonsillectomies, *Arch Int Med* **27** 631 (June) 1921

2 Mullin, W. V. An Analysis of Some Cases of Tubercles in the Tonsil, *J A M A* **80** 1211 (April 28) 1923

3 MacCready, P. B., and Crowe, S. J. Tuberculosis of the Tonsils and Adenoids. A Clinical and Roentgen-Ray Study of Fifty Cases Observed for Five Years After Operation, *Am J Dis Child* **27** 112 (Feb) 1924

4 Howarth, Walter G., and Gloyne, S. R. The Nature and Path of Infection in the Tonsils, *J Laryng & Otol* **39** 429 (Aug) 1924

5 Scarff, Gordon R., and Whitby, L. E. H. The Incidence of Tuberculous Infection in the Faucial and Pharyngeal Tonsils of Children, *J Laryng & Otol* **43** 328 (May) 1928

Wilkinson⁶ and Rossner⁷ have reported series which can be compared with those studied in this laboratory, since their cases were not selected but represented the routine examination of tonsils of subjects in all age groups. For 600 pairs of tonsils removed in 1900 Wilkinson found the incidence of tuberculosis to be 1.33 per cent, but only 0.5 per cent for 10,000 tonsils removed from 1923 to 1927. Rossner reported the diagnosis of tuberculosis in 1.01 per cent of 296 cases, the ages varying from 2 to 61 years.

In view of the decreased incidence of most forms of tuberculosis, particularly those of the respiratory tract, it became desirable to determine whether the incidence of tonsillar tuberculosis also has decreased in the material examined in this laboratory. Wilkinson⁶ has shown such a change in the material at the Mayo Clinic. For this purpose the

Incidence of Tuberculosis in Tonsils, 1933 to 1935

Age Groups, Years	All Cases			Faucial Tonsils			Pharyngeal Tonsils		
	Number	Number of Tuber- culous Tonsils		Number	Number of Tuber- culous Tonsils		Number	Number of Tuber- culous Tonsils	
			Incidence, %			Incidence, %			Incidence, %
0-5	727	2	0.27	717	1	0.14	637	2	0.31
6-10	1,689	9	0.53	1,669	8	0.48	1,450	4	0.28
11-15	1,211	5	0.41	1,206	4	0.33	982	0	0.00
16-20	763	3	0.39	761	3	0.40	290	0	0.00
21-30	643	5	0.78	643	5	0.78	49	0	0.00
31-40	241	1	0.41	241	1	0.41	18	0	0.00
41	263	1	0.38	263	1	0.40	12	0	0.00
Age unknown	817	2	0.24	817	1	0.12	430	1	0.23
Total	6,359	28	0.44	6,317	24	0.38	3,863	7	0.18

specimens obtained at 6,280 tonsillectomies, which were performed during the years 1933 to 1935, were reviewed, and the results were summarized in order to make them comparable to the series of 8,697 specimens studied prior to 1921 (Weller¹).

The technic used in the preparation of these tonsils for microscopic examination was that outlined by Weller in 1921: fixation in solution of formaldehyde, bisection of the tonsil in a vertical plane at right angles to the mucous surface and microscopic examination of a section representing the entire cut surface, after the tissue had been embedded in paraffin and stained with hematoxylin and eosin. As was appreciated in 1921 there is an error in examining only one section of a tonsil, even

6 Wilkinson H. Fielding. Pathologic Changes in Tonsils. A Study of Ten Thousand Pairs of Tonsils with Special Reference to the Presence of Cartilage, Bone, Tuberculosis and Bodies Suggestive of Actinomycosis, Arch Otolaryng **10** 127 (Aug.) 1929.

7 Rossner, Therese. Häufigkeit und Bedeutung der Tonsillentuberkulose, Arch f. Ohren-, Nasen- u. Kehlkopfh **135** 214, 1933.

though it is an optimum section. The method employed, however, is the only one suitable for the routine examination of a large quantity of material.

The results of this study are summarized in the accompanying table, which is self-explanatory. The incidence of tuberculosis in the faucial tonsils in the various age groups showed some variation, the lowest (0.27 per cent) being in the youngest age group (0 to 5 years), while the highest (0.78 per cent) was found in the age period from 21 to 30 years. During the age period of 6 to 10 years tubercles were present in 0.53 per cent of cases. The other age groups showed a rather constant incidence of tonsillar tuberculosis, varying only from 0.38 to 0.41 per cent. No involvement of the pharyngeal tonsils was noted in subjects more than 10 years of age. The percentage of tuberculosis found in all tonsils and that in the faucial tonsils were very similar, 0.44 and 0.38 per cent, respectively, but the incidence of tuberculosis of the pharyngeal tonsils was very low, only 0.18 per cent.

A definite decrease in tonsillar tuberculosis was noted, the incidence for the years 1933 to 1935 being 0.44 per cent, as compared with 2.35 per cent for the years 1906 to 1919. Since these results were based on the comparatively large series of 6,359 and 8,697 cases, respectively, and since the methods of examination were exactly the same in the two groups, the results are highly significant. The trend toward a lower incidence, which Weller¹ noted (3 per cent in 1917 and 2.35 per cent in 1920), has continued to the present time. The reduced incidence of tonsillar tuberculosis was apparent in all age groups.

CHEST LEADS IN ELECTROCARDIOGRAPHY

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At first sight it seems surprising that the electrocardiogram was not derived precordially from the beginning, i e., as directly as possible. However, the fact that it was not is not so strange, for the limb leads give almost constant pictures, while chest leads show distinct changes when the exploring electrode is shifted. Moreover, the standard leads of Einthoven are adequate for a study of arrhythmia, and the problem of irregularity of the pulse has for many years been the leading one in cardiology. Though chest leads were used occasionally in the early days of electrocardiography,¹ their value was not generally appreciated until electrocardiographic research was made subservient to examination of the myocardium, at first especially in coronary thrombosis. It is to the credit of Wood and Wolferth and their co-workers² to have shown in a number of papers that a fourth lead may sometimes supply information of value in the diagnosis of coronary thrombosis when the classic leads either are failing or do not give sufficiently obvious information.

However, not alone in coronary thrombosis do the three standard leads occasionally show a picture from which it is impossible to draw conclusions. In other disorders of the myocardium or of the coronary arteries the clinical picture, the evaluation of which should have the preference, can in the same way conflict with the electrocardiographic data.

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1 Einthoven, W. *Arch. internat. de physiol.* **4**: 132, 1906. Waller, A. D. *J. de physiol.* **8**: 229, 1887. Lewis, T. *Heart* **7**: 127 and 293, 1920, **8**: 193, 1921. Ackermann, R. *Deutsches Arch. f. klin. Med.* **144**: 61, 1924.

2 (a) Wolferth, C. C., and Wood, F. C. *Am. J. M. Sc.* **183**: 30, 1932, *M. Clin. North America* **16**: 161, 1932. (b) Wood, F. C., and Wolferth, C. C. *J. Clin. Investigation* **11**: 815, 1932, *Experimental Coronary Occlusion*, *Arch. Int. Med.* **51**: 771 (May) 1933. (c) Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C. *Electrocardiographic Study of Coronary Occlusion*, *ibid.* **52**: 752 (Nov.) 1933. (d) Wood, F. C., and Wolferth, C. C. *Am. Heart J.* **9**: 706, 1934. (e) Wolferth, C. C., Wood, F. C., Bellet, S., and Edeiken, J. *Tr. A. Am. Physicians* **49**: 223, 1934. (f) Wolferth, C. C., and Wood, F. C. *Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of Left Ventricle*, *Arch. Int. Med.* **56**: 77 (July) 1935.

Since November 1933 we have as a rule used a chest lead in addition to the three standard leads. After having studied about one thousand, five hundred electrocardiograms obtained in this way, the value of such a "semidirect" lead in solving various electrocardiographic and clinical problems became evident. Thus the thoracic electrocardiogram, which often indicates damage of the myocardium by deviation of the T wave³ in essential hypertension, chronic nephritis and coronary sclerosis, may teach new facts,⁴ the question of the evaluation of the T waves in strong left or right axis deviation may be partly solved by the aid of the chest lead,⁵ and finally this lead supplies data for a study of bundle branch and aiborization block⁶.

TECHNIC

The greater part of our curves were taken in such a way that the right arm electrode was applied above the area of absolute dulness of the heart in the fourth intercostal space to the left of the sternum, while the left arm electrode was applied to the back, mesial to the inferior angle of the scapula. This lead corresponds more or less with lead IV of Wood and Wolferth, except that these authors applied the right arm electrode above the cardiac apex. Later we^{4a} proceeded to apply the left leg electrode above the dulness of the heart and the right arm electrode to the left leg. Since the place of the nonexploring electrode is of little influence on the form of the electrocardiogram,³ the same picture is obtained, except that it is a mirror picture with the P and T waves normally positive. Finally we applied the negative electrode on the left leg and the right arm electrode over the area of dulness of the heart, for it appeared to us that in the last lead but one several characteristics of deviating curves, especially in coronary thrombosis and in chronic nephritis, were less striking than in the inverted lead. In this last lead the P and T waves are therefore normally negative. All curves have been checked in such a way that 1 mm equals 1 millivolt. Overshooting was prevented, while slackening did not exceed one fiftieth of a second.

1 THE NORMAL ELECTROCARDIOGRAM IN THE CHEST LEAD (FIG 1A)

As the figures found by us are practically the same as those reported by other investigators,⁷ we shall not publish the tables referring to them. We believe, as will appear from what follows, that in the chest lead a negative or positive monophasic ventricular complex, a ventricular

3 Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S. *Am Heart J* **9** 447, 1934. Footnotes 1 and 2.

4 (a) van Nieuwenhuizen, C. L. C. *Wien Arch f inn Med* **29** 25, 1936. (b) Master, A. M. *Am Heart J* **9** 511 (April) 1934. (c) Katz, L. N., and Kissin, M. *ibid* **8** 595, 1933. (d) Goldbloom, A. A. *Am J M Sc* **187** 489, 1934. (e) Bohning, A., and Katz, L. N. *ibid* **189** 833, 1935.

5 (a) Barnes, A. R., and Whitten, M. B. *Am Heart J* **5** 142, 1929. (b) van Nieuwenhuizen, C. L. C., and Hartog, H. A. P. *ibid*, to be published.

6 Wilson, F. N. *Heart* **16** 155, 1933.

7 Master^{4b} Katz and Kissin^{4c} Goldbloom^{4d} Bohning and Katz^{4e}

complex which is too broad or the failing of the Q or of the R wave is just as pathologic as a difference of level between the ST and the PQ segment greater than 2.5 mm or a flat diaphasic or inverted T wave, except in a long sheep heart or the heart of a child (see section 3). Sometimes clinical importance must be attached to the origin of a flat or diaphasic P wave.

CHANGES DUE TO CORONARY THROMBOSIS

Wood and Wolferth^{2c} divided the tracings obtained by them in this disease into two groups. In the first group—tracings divided thoracically in anterior infarctions—the electrocardiogram shows a difference of level between the depreciated ST segment and the iso-electric line, which is large and remains longer than in the other leads. In the course of time a positive T wave arises. The Q wave is either absent or very small. Usually it appears that the RS-T segment in lead I runs higher than normal, sometimes the RS-T segment in lead III lies lower than normal. In the second group—tracings in posterior

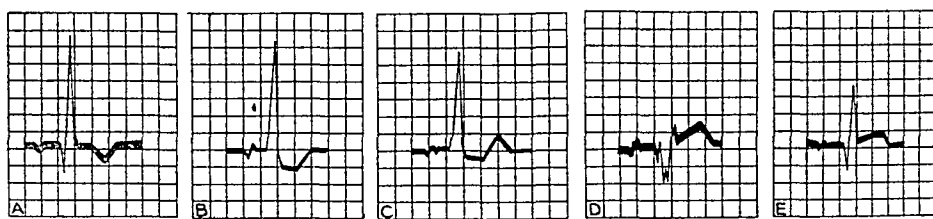


Fig 1—A, a normal electrocardiogram, B and C, the C 2 type of tracing, D and E, the C 1 type of tracing

infarctions—the electrocardiogram does not properly show a typical deviation in the chest lead. Sometimes there is a slight difference of level between the ST segment and the iso-electric line, and sometimes there is a flat or positive T wave. The deviations should be searched for rather in lead II, where the ST segment is nearly always elevated and a negative T wave arises in the long run, in lead III a deep Q wave usually is seen which satisfies the criteria fixed by Pardee.

However, in our opinion a depression in the course of the RS-T interval in the chest lead cannot be considered a characteristic of coronary thrombosis, as the same deviation may be seen in coronary sclerosis, essential hypertension and chronic nephritis. Neither is a positive T wave a typical feature, as it is seen in many deviations of the myocardium. Wood and Wolferth^{2d} have described the occurrence of very high T waves in the thoracic electrocardiogram, which, remarkably, were found especially in cases of mild involvement. We too saw this peculiarity several times (see the case reports which follow), though it is an open question whether such high T waves would not be found

more often in the course of coronary thrombosis if the surface of the chest were accurately explored with the electrode

Finally, Wood and Wolferth and their colleagues⁴ pointed to the importance in the diagnosis of coronary thrombosis of a small deflection directed upward at the beginning of the ventricular complex. However, we saw this "initial upward deflection" also in cases in which coronary thrombosis could be ruled out

Referring to our own material, the thoracic electrocardiograms obtained in cases of coronary thrombosis may be divided into the two following types, which we call the C 1 and C 2 types⁸

1 The C 2 type (fig 1 B and C) This type, which to a certain extent resembles that of the first type described by Wood and Wolferth has for its particularity *a flat or slightly concave descending ST segment, proceeding at a pronounced angle (usually 125 or 130 degrees) into an ascending line*, which continues into a positive T wave or in the iso-electric line. The ST line may run far under the iso-electric level but also may rise from it. The positive T wave may be lacking, though it usually appears in the course of the disease. The Q summit may be missing, but sometimes it is obvious. The P summit is sometimes negative before thrombosis occurs and diphasic afterward. A notch in the ventricular complex is sometimes missing in the lead used by us, but if the cardiac region is explored with the anterior electrode, it is usually found. In the course of coronary thrombosis a high T wave in the chest lead and also in leads II and III may appear in connection with this type of thrombosis. Usually an acute stage of pain, anxiety or dyspnea was noted in the history of a patient with this type of electrocardiogram, and often there was a long history of angina pectoris. Once this type of tracing was found in a case of diabetes mellitus and syphilis (case 4, table 1)

It is important to retrace changes in the standard leads that are typical of coronary thrombosis and to observe what localization they admit. Three times a W-shaped ventricular complex occurred in lead I, twice a Paidee Q wave occurred in lead III. The W-shaped ventricular complex acquired a sharp negative T wave after some time and the Paidee Q wave remained. In the four other cases no characteristic alterations were seen, *thus the thoracic lead offered here the only secure electrocardiographic diagnostic evidence*^{8a}

According to Baines and Whitten⁵ the sharp negative T wave in lead I which follows the stage of the W-shaped complex must be

8 The types are described for the right arm electrode (heart dulness) and the left leg electrode

8a Since the preparation of this article this view has been confirmed. Especially in cases of mild coronary thrombosis, lead IV often offers the only deviations

ascribed to anterior infarction, which corresponds with our view that the C 2 type is characteristic of infarction in the anterior wall^{8b}. On the other hand, according to Wilson⁶ the occurrence of a Pardee Q wave in lead III (Q III type) is characteristic of infarction of the posterior wall, which is in contradiction with our experiences with curves of this form. Nevertheless, one must be very careful when judging a Pardee Q wave. When this picture is seen to arise (e g, together with violent substernal pain), this is of far greater value than a deep Q wave in lead III that is already present, which may occur also in coronary sclerosis without myocardial infarction (Willius⁹ and Pardee¹⁰).

2 The C 1 type of tracing (fig 1 D and E). This type, which up to now has not been described in the literature on chest leads, exists in its most perfect form (fig 1 D) in the ventricular complex in which are notable an *"initial upward deflection"*, a deep Q wave, a notch in the Q wave and especially an ST line with a high take-off that goes on convexly and into which creeps the T wave. Unlike the C 2 type, this type as a rule shows a pronounced Q wave. The small notch directed upward may be missing, but it may occur in the C 2 type and may therefore be valued only in connection with the other deflections. The most characteristic point is the high and convex course of the RS-T segment as it is seen in anterior infarction in lead I, but usually it is less definite. In other cases the ST segment becomes flat but keeps on rising too high and runs above the iso-electric level (fig 1 E). As a rule the following more or less typical alterations are found in the other leads.

Lead I. An absolutely or relatively too deep S wave and a low T wave.

Lead II. A too broad ventricular complex, notches in R, S or RS and a too deep S wave, the PQ distance is always too long.

Lead III. A too deep S wave, notches after the S wave, a flat diphasic or negative T wave and sometimes a Pardee Q wave, a high take-off of the convex ST segment (Pardee RS-T wave) or a W-shaped or M-shaped ventricular complex.

It is notable that in the history of patients who show electrocardiograms of this type an acute moment is usually missed and that sometimes (case 5, section 1) the alterations are seen to arise gradually in the course of time. It is our opinion that these electrocardiographic

8b Afterward in three other cases the postmortem examination proved the diagnosis to be correct.

9 Willius, F. A. *Deutsches Arch f klin Med* **172** 113, 1931.

10 Pardee, H. E. B. An Electrocardiographic Sign of Coronary Artery Obstruction. *Arch Int Med* **26** 244 (Aug) 1920.

alterations are probably due to posterior infarction. In favor of that theory the following reasons may be cited:

1 Alterations typical of coronary thrombosis are seen in the other leads, especially in lead III, which indicates posterior infarction, according to Baines and Whitten and to Wilson.

2 The broad ventricular complexes, which have approximately the shape of an alternization block, and the lengthened or maximal atrio-ventricular conduction time, which are *always* found in this form, must be ascribed, as far as our knowledge goes, to alterations in the circulation of the posterior coronary artery.¹¹

3 A negative reason is the absence of deviations characteristic of coronary thrombosis in lead I.

4 About the same form is sometimes seen in ventricular extrasystoles in the chest lead, when ventricular systoles of the left type exist in leads I and III (fig 4E).

It is possible that in some such manner as is herewith suggested the problem of anterior infarction, which usually occurs suddenly, and posterior infarction, which usually appears gradually as the result of increasing coronary sclerosis, concerning which there is considerable controversy, may be settled. Clinicians have always had the impression that anterior infarction occurs much oftener than posterior infarction, whereas many workers in pathologic anatomy have found an equal division of thrombosis of the left and of the right coronary artery. Perhaps posterior infarctions escape clinical observation, an attack of dyspnea or a moderate attack of angina pectoris may be caused by coronary thrombosis. There is no certainty about it, however, as none of the patients have died and postmortem inspection has not been possible.^{11a} According to other writers (Wood and Wolferth and Jervell) posterior infarction does not supply typical data. According to them it is only by means of the chest lead, which is indeed "semidirect," that alterations of the anterior parts of the heart and especially of the cardiac apex (which is situated nearest to the electrode) become electrocardiographically visible. On the other hand our patients, though not showing the extensive typical picture of coronary thrombosis, were suspected of having it, and in connection with the C 1 type we found typical pictures only in the third standard lead. Finally, it is possible that the C 1 type is caused by septal infarction, due to insufficiency of either the left or the right coronary artery. In the first case anterior

11 Spalteholz, W. Verhandl. d. anat. Gesellsch. **21** 141, 1907. Jamin and Merkel. Die koronaren Arterien des menschlichen Herzens, Jena, Gustav Fischer, 1907. Hans. Anat. Hefte **43** 627, 1911. Taterka, H. Klin. Wchnschr. **5** 1833, 1926. Frank. Ztschr. f. Kreislaufforsch. **21** 664, 1929.

11a. Lately in a case of acute posterior infarction (confirmed) a similar curve was found (Q wave of 20 mm., a very high take-off of the convex ST segment).

infarction of the septum should arise, with possible infarction of parts of the left ventricle and of the apex, in the second case posterior infarction of the septum should arise, with or without infarction of the right ventricle. Considering the deviations in the other leads, we believe

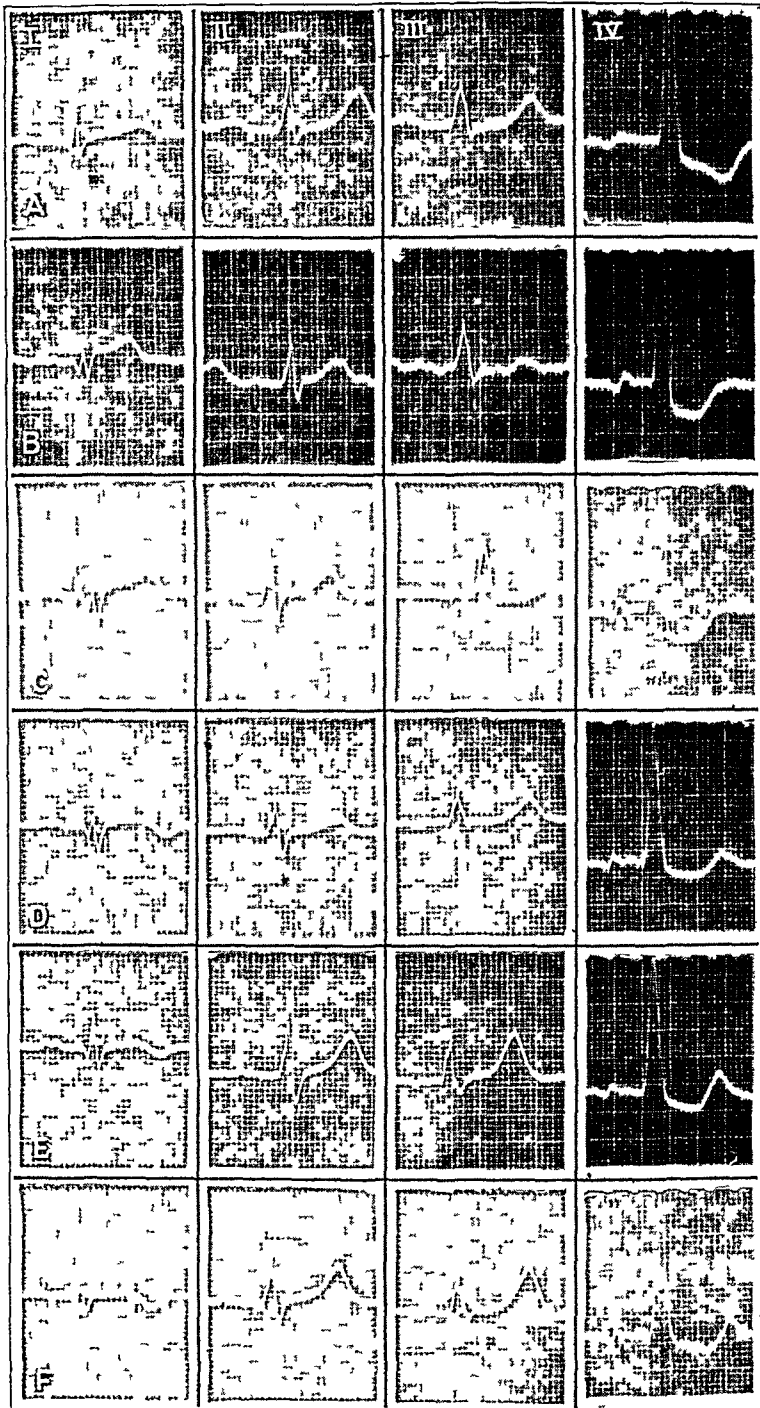


Fig 2—Examples of the C 2 type of tracing in case 1, section 1 (table 1, case 1) A was taken on Jan 30, 1934, B on February 2, C on February 3, D on February 12, E on May 1 and F on April 7, 1935

that the C 1 type is the expression of infarction of the posterior wall of the heart or perhaps in the posterior part of the ventricular septum

On one occasion we saw a C 1 type, though a less obvious one, in a case of rheumatic myocarditis (case 7, table 2, fig 6 D)

In summary, two deviations of the thoracic electrocardiogram are described which are typical of anterior infarction (the C 2 type), on the one hand, and most probably of posterior infarction (the C 1 type), on the other. If the W-shaped ventricular complex in lead I is considered to be typical electrocardiographic evidence of anterior infarction and if the occurrence of it in lead III is considered to be characteristic of posterior infarction, then in eight of fourteen cases the diagnosis was established with the standard leads. In six cases the chest lead offered the only pathognomonic evidence, and in several cases the thoracic electrocardiogram was typical when in the course of the disease the standard leads became more and more normal. The following cases are illustrative

CASE 1 (table 1, case 1, fig 2 A to F) —A bookkeeper aged 52, who had never been seriously ill before, suddenly had an attack of violent pain in the cardiac region. At his own request he was taken immediately to the hospital, where a diagnosis of coronary thrombosis was made. During his stay he recovered entirely. An electrocardiogram made half an hour after the beginning of the initial attack (fig 2 A) showed some deviations in the course of the RS-T interval in the three standard leads, these, however, were not typical. In the chest lead the C 2 type was seen. After forty-eight hours a W-shaped ventricular complex was noted in lead I, with an arcuate ST segment (fig 2 B). Later a negative T wave arose, which in the course of sixteen months returned to a flat T wave (fig 2 C to F). In leads II and III the T waves became very high after fourteen months (fig 2 E). Finally the ST segment took off iso-electrically in lead IV, but its course remained typical of the C 2 type, in the meantime typical changes were no longer seen in the other leads. This case proves that in very early stages the chest lead may be the only electrocardiographic sign of coronary thrombosis. It proves also that the unchangeable characteristic lies in the course of ST and not alone in the take-off of ST or in a positive T wave.

CASE 2 (table 1, case 5, fig 3 D to E) —Two days prior to his admission to our clinic a mason aged 43 had a sudden pain in the chest. When he was admitted to the clinic the pulse rate was 88 and the temperature 38 C (100.4 F), but most striking was the violent dyspnea. On percussion the heart appeared to be dilated somewhat to the left. For several hours slight pericardial friction was heard. Swallowing was painful. The differential diagnosis lay between coronary thrombosis and diaphragmatic pleuritis. The roentgenogram did not indicate an existing pleuritis, but there were deviations in the electrocardiogram. A Paidee Q wave warned us to be careful and in lead IV a C 2 type appeared to be present, with a deep Q wave (fig 3 D). The man soon recovered and was discharged at his own request. Probably pericardio-pleuritis was the correct diagnosis, with pleuritis the cause of the most serious complaints. This case teaches the value of the chest lead in making a difficult differential diagnosis in a case of acute intrathoracic disease. Thus there was found, besides the electrocardiographic characteristics of anterior infarction, a very deep Q wave in lead IV. Theoretically it is possible that this last-mentioned deviation existed as the remainder of posterior infarction; absolute certainty could of course not be obtained.

TABLE 1—Data for Patients Included in Section One with C 2 Type of Tracing

Case	Sex	Age	Deviations in Lead I	Deviations in Lead II	Deviations in Lead III	Deviations in Lead IV	Diagnosis and Comments
1	M	52	W shaped QRS complex	ST aniso electric, high T waves occurred later	Notches, high T waves later	O 2 type	Coronary thrombosis (case 1, section 1, fig 2 A to F)
2	M	43	W shaped QRS complex	No typical deviations	ST marked aniso electric	O 2 type	Coronary thrombosis (fig 3 A)
3	M	62	T diphasic, R 19 mm	R low, notch in RS	Deep S	C 2 type	Coronary thrombosis, 4 years ago severe substernal pain, same complaints 14 days ago (fig 3 B)
4	M	64	T deep inverted, R 18 mm	T negative, notch in RS	S too deep	C 2 type	Diabetes mellitus, progressive paralysis (case 5, section 1, fig 3 O)
5	M	43	ST aniso electric	Notch in R	Pardee Q	O 2 type	Coronary thrombosis (case 2, section 1, fig 3 D and E)
6	M	42	T negative, diphasic	T diphasic	Notch in RS T flat	C 2 type	Syphilitic aortic regurgitation (?), coronary thrombosis (case 3, section 1)
7	M	56	ST aniso electric, T negative	T deep, inverted	Pardee Q, T deep inverted	C 2 type	Chronic articular rheumatism, attacks of pain in left and right arm last month, coronary occlusion ?
8	M	65	ST aniso electric, T flat	T diphasic	Queer QRS complex	O 2 type	Coronary thrombosis, 14 days after attack of severe substernal pain
9	M	52	Low W shaped QRS complex	ST aniso electric	ST aniso electric	C 2 type	Coronary thrombosis (case 4, section 1, fig 4 A to D)
10	F	38	T low, ST aniso electric	T low, ST aniso electric	T diphasic	C 2 type	Coronary thrombosis? (severe attack of substernal pain several months ago)
11	M	59	T trace	No deviation	ST high take off	O 2 type	Coronary thrombosis 2 months ago, angina pectoris last year
12	M	75	W shaped ventricular complex	Notch in R	Small ventricular complex, T low	O 2 type	Coronary thrombosis 1 month ago, since then dyspnea on exertion

CASE 3 (table 1 case 6) —A man aged 42 had been complaining for six weeks of pain in the right arm and palpitation on exertion. Ten days prior to his admission to the clinic he suddenly had a violent pain in the abdomen, the temperature rose and he sweated profusely. Three years before he had been in a hospital, and a diagnosis of syphilitic aortic insufficiency had been made (the Wassermann reaction of the blood was ± 4 and the Sachs-Georgi test was positive). On

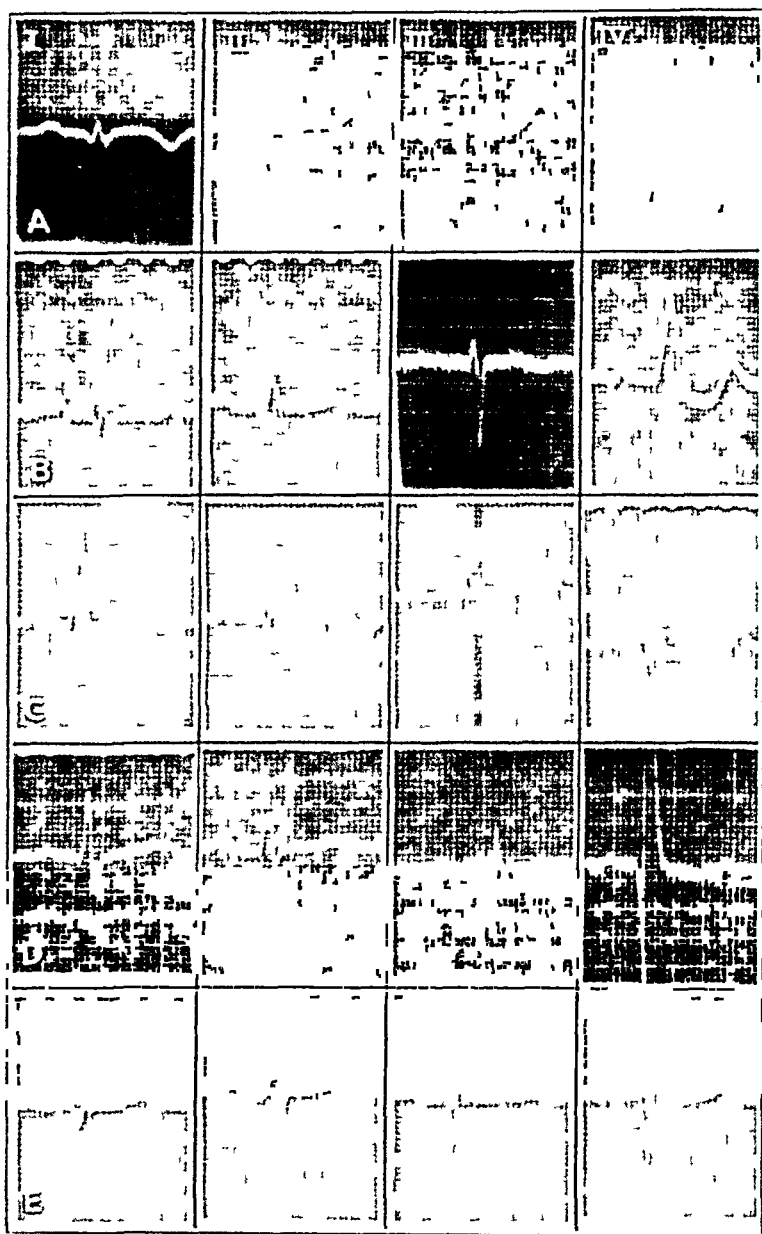


Fig. 3—Examples of the C 2 type of tracing. For data on *A* see table 1, case 2, for *B* see table 1, case 3, for *C* see case 5 (section 1) and table 1, case 4, for *D* and *E* see case 2 (section 1) and table 1, case 5.

examination the following conditions were diagnosed: aortic insufficiency and cerebrospinal syphilis (the Wassermann and Sachs-Georgi reactions being negative). The pulse rate was 84, the temperature 37.7 C (100 F) and the respiratory rate normal. The sedimentation rate of the erythrocytes was normal. There were

TABLE 2—Data for Patients Included in Section One with C 1 Type of Tracing

Case	Sex	Age	Deviations in Lead I	Deviations in Lead II	Deviations in Lead III	Deviations in Lead IV	Diagnosis and Comments
1	M	65	S too deep, T low	Broad QRS complex, A V conduction time 0.2 sec, notches	Broad QRS complex	C 1 type	Coronary thrombosis (case 6, section 1 fig 5 A)
2	M	65	S too deep, T low	A V conduction time 0.2 sec, notches	Paradee Q, T trace	C 1 type	Coronary thrombosis ? (case 7, section 1 fig 5 B)
3	M	51	S too deep, T low	A V conduction time 0.2 sec, notch in RS	Broad complex, T negative, notches	C 1 type	Aortic regurgitation and aneurysm, coronary stenosis (case 8, section 1, fig 5 C)
4	M	69	S too deep, T low	A V conduction time 0.19 sec, notch in R T diphasic	Slight W shaped complex	C 1 type	Coronary thrombosis (case 9, section 1, fig 5 D and F)
5	F	70	ST 3 mm lower than PQ, T diphasic, ST concave	Small QRS complex, ST concave, notch in R	"Paradee RS type", deep S	C 1 type	Gradually increasing coronary sclerosis (case 10, section 1, fig 6 A to C)
6	M	70	S too deep, broad QRS complex	A V conduction time 0.2 sec, S too deep, notch after S	S too deep, ST anisoelectric	C 1 type	Coronary thrombosis 8 days previously (fig 6 E)
7	F	19	S too deep, T diphasic notch in RS	ST concave	Notch in R, T diphasic	C 1 type	Acute polyarticular rheumatism, pericarditis (case 11, section 1, fig 6 D)

that it arose at the time of the first attack of oppression through coronary thrombosis or which seems more probable to us gradually as a result of coronary sclerosis

CASE 7 (table 2 case 2 fig 5B)—This man aged 65 had an interesting history. On Jan 7 1932 he suddenly had a violent pain in the left side which radiated to the upper portion of the abdomen this pain lasted for a day and a half. He was short of breath, and deep breathing was painful. His physician considered

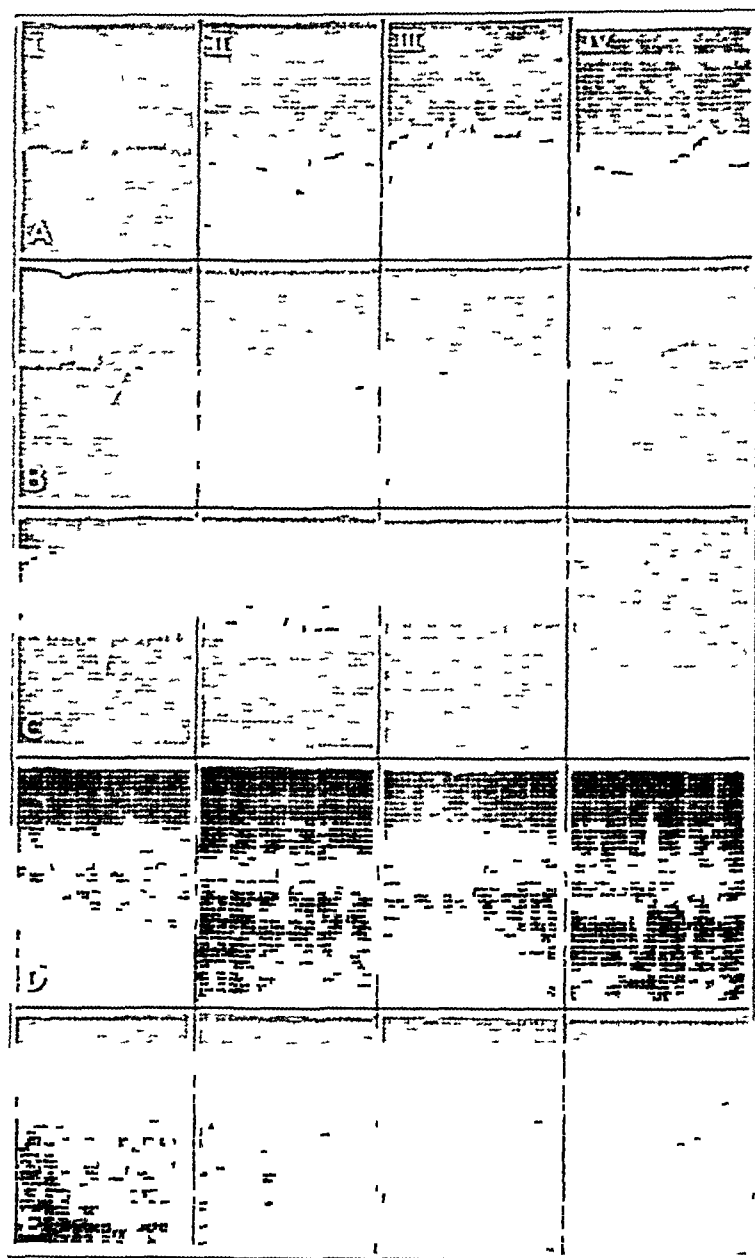


Fig 5—Examples of the C 1 type of tracing. For data on A see case 6 (section 1) and table 2 case 1 for B see case 7 (section 1) and table 2, case 2, for C see case 8 (section 1) and table 2 case 3 and for D and E see case 9 (section 1) and table 2, case 4

that he had heart disease. After some time pleuritic friction became audible, and he was sent to our clinic the diagnosis being pleuritis. At the time of admission to the clinic he had a slight fever (temperature of 38.2 C, 101 F) the respiratory

rate was 26 per minute and the pulse was slightly unequal and irregular, with a rate of 108. The blood pressure was 140 systolic and 90 diastolic. At the base of the left lung there was slight pleuritic friction, with pericardial friction of the heart, which was somewhat dilated to the left. An electrocardiogram was not made at the time. The sedimentation rate was strongly increased after one hour 72 mm and after two hours 92 mm. There was slight leukocytosis (9,800 leukocytes). On the roentgenogram rests of old specific deviations were seen. The temperature soon became normal and the pain disappeared. Tubercle bacilli were never found in the sputum, but a diagnosis of pleuritis sicca and pulmonary tuberculosis was made. The patient was discharged in fairly good condition, but after five weeks he was readmitted to the clinic. He no longer coughed, but the shortness of breath had become more pronounced. A few days prior to his readmission to the clinic he had had another attack of pain, in the right side this time, and he had coughed up some bloody sputum. Examination showed that dyspnea was marked and that both legs were edematous. The respiratory rate was 40 per minute, the pulse rate 120 and the temperature 38.6 C (101 F). The percussion sound was dull at the base of the right lung, and on auscultation crepitant rales were heard. Again a diagnosis of pulmonary tuberculosis was made, and the patient was discharged. On Dec 7, 1933, he was readmitted to the clinic because of general cardiac failure. At that time an electrocardiogram showed a C 1 type of tracing in lead IV and the previously mentioned characteristic changes in the standard leads. In our opinion the history of the case should be interpreted as follows. On his first admission to the clinic the patient had coronary thrombosis (with pleuropericarditis), on his second admission infarction of the lungs and on the third admission cardiac failure caused by myodegeneration. This case clearly shows the value of the chest lead in studying acute intrathoracic processes.

CASE 8 (table 2 case 3, fig 5 C) —A patient with an aortic aneurysm and syphilitic aortic regurgitation had had attacks of oppression for six years. There was progressive failure of the heart. An electrocardiogram showed changes of the C 1 type of tracing, probably caused by coronary stenosis due to syphilis of the aorta. As there was no acute moment recorded in the anamnesis, acute coronary obstruction probably had not occurred.

CASE 9 (table 2, case 4 fig 5 D and E) —This man aged 69 had a sudden violent sense of oppression in the cardiac region but no pain. After that he grew short of breath, and cardiac failure arose. On examination the heart appeared to be dilated to the left and to the right. There was a systolic murmur at the apex. The pulse rate was 70, the respiratory rate 26 and the temperature normal. The blood pressure was 120 systolic and 85 diastolic. The liver was palpable. There was slight jaundice. An electrocardiogram showed the typical changes of the C 1 type of tracing in all leads. In lead III no Pardee Q wave was visible, but there was a small W-shaped ventricular complex, similar to that seen in anterior infarction in lead I. The anamnesis and the electrocardiogram established the probable diagnosis of coronary thrombosis.

CASE 10 (table 2, case 5, fig 6 A to C) —Since November 1933 a woman aged 70 had repeatedly been admitted to the hospital. The diagnosis was arteriosclerotic myodegeneration with severe cardiac failure. Angina pectoris occurred at the least exertion. The heart was enormously dilated to the left and to the right, and there was congestion of the lungs. The blood pressure was 210 systolic and 105 diastolic. During the observation the electrocardiogram showed a picture which became gradually clearer and which showed in the standard leads more and more definitely the deviations of posterior infarction. Also there were changes in the chest lead, in which a C 1 type of tracing was obtained showing a small ventricular

complex. In our opinion the myocardial infarction arose, without any acute stage, from the gradually increasing coronary sclerosis, in which the posterior branch of the coronary artery was chiefly involved (lead IV was taken with the electrodes changed)

CASE 11 (table 2, case 7, fig 6 *D*)—A girl aged 19 years was admitted to the hospital because of dyspnea. A few years before she had suffered from a second

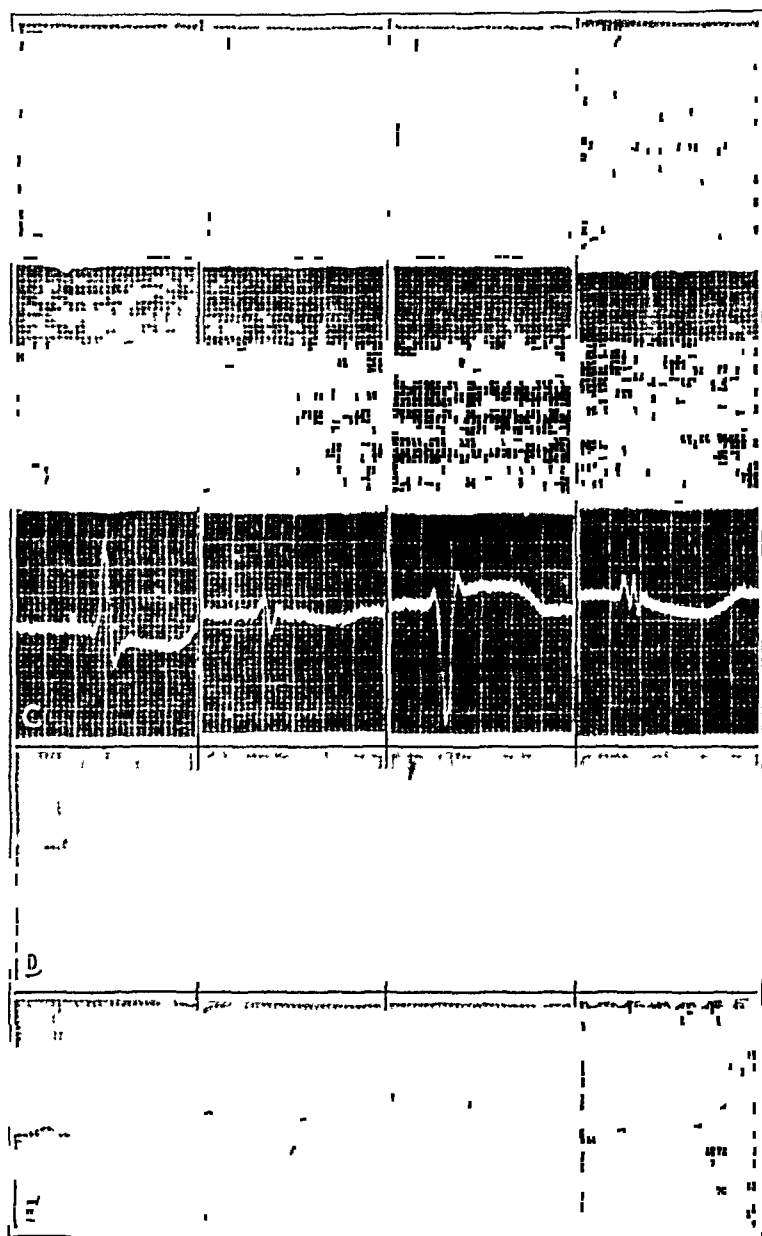


Fig 6—Examples of the C 1 type of tracing. For data on *A* to *C* see case 10 (section 1) and table 2, case 5. *A* was taken on Nov 17, 1933, *B* on Oct 3, 1934, and *C* on Sept 3, 1935 (the electrodes were in the precordium and on the left leg). For data on *D* see case 11 (section 1) and table 2, case 7, and for *E* see table 2, case 6.

attack of acute articular rheumatism (the first attack had occurred five years previously). Examination revealed enlargement of the heart, with dilatation to the left and to the right, of the mitral type. The liver was enlarged and had a blunt

margin. Slight edema was present. The patient's condition rapidly became worse (for a few days before her admission to the clinic pericardial friction had been audible), and about two months later she died. At autopsy, 200 cc of fluid was present in the pericardium. There was fresh endocarditis of the mitral valve, and many rheumatic nodes were spread over the myocardium. It is well known that in rheumatic myocarditis the electrocardiographic picture in the standard leads may be reminiscent of coronary thrombosis, as demonstrated in this case by the chest lead.

2 ABNORMALLY DEEP T WAVES

While taking thoracic electrocardiograms with the anteroposterior or anterior-left leg lead (in which normally the T wave is negative) we sometimes saw remarkably deep T waves, and it seemed important to ascertain the clinical significance of this deviation. Master^{4b} reported the following values for the T wave in normal subjects: average, —3.3 mm, minimum, —1.5 mm, and maximum, —7.5 mm. Bohning and Katz^{4c} found —5.7, —2 and —10 mm, respectively, and Goldbloom^{4d} found —4.9, —2 and —8 mm, respectively. The maximum values reported by Bohning and Katz (—10 mm in twenty-five cases) were highest, and those reported by Master (—7.5 mm in one hundred and four graphs) were lowest. We too found in some cases —10 mm as a maximum depth for the T wave in a normal subject, nevertheless, such a value is exceptional. In the next paragraphs T waves deeper than 10 mm in the chest lead will be discussed.

Bohning and Katz found in 12 per cent of their curves for patients with a suspected or distinctly insufficient coronary circulation a T wave of from —8 to —11 mm. Wolferth and Wood,^{2f} who sometimes found a high T wave in the chest lead in cases of anterior infarction, expected to find a very deep T wave in cases of posterior infarction. However, they have not described such a case as yet and their supposition does not seem probable to us (see section 1). As far as we have been able to see, no attention has been paid to an abnormally deep T wave in association with other conditions. It has been pointed out by some investigators that the position of the anterior electrode influences the size of the T wave (Hoffman and Delong¹² and Roth¹³). For patients suffering from cardiac disease a deep T wave should be of significance only when the anterior electrode is in a certain position. According to these investigators the T wave increases in depth as the anterior electrode is applied nearer to the sternum, and according to Katz and others this happens when the exploring electrode is applied nearer to the cardiac apex. We also observed this in a series of electrocardiograms of normal subjects (generally the T wave increases in depth

12 Hoffman, A. M., and Delong, E. Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Damage, *Arch Int Med* 51: 947 (June) 1933.

13 Roth, I. R. *Am Heart J* 10: 798, 1935.

from the first intercostal space, where it is still positive, as a rule, to lower down, and the same occurs when the exploring electrode is moved from left to right in one intercostal space) Nevertheless, we found that those variations never reach values exceeding 10 mm, so that great importance may be attached to a T wave deeper than 10 mm

Another question is how far changes of the anatomic axis of the heart influence the thoracic electrocardiogram¹⁴ Einthoven and his co-workers¹⁴ and later Cohn and Raisbeck¹⁵ demonstrated that inversion of the T wave may be brought about by changing the angle between the horizontal and the anatomic axis One can imagine that such a mechanism played a part in our cases in which there were abnormally deep T waves But on measuring the previously mentioned angle (on the roentgenograms of nearly all patients) we could not find any conformity between the anatomic axis and the changes in the T wave Then there remains the possibility that a deep T wave may be caused by a revolving of the heart on its anatomic or horizontal axis In opposition to this theory may be stressed that fact that *various* valvular defects (stenosis or insufficiency of the aorta or of the mitral valves) are attended with such a deep T wave

However that may be it is of greater importance that we found organic cardiac or cardiovascular disease in forty of our forty-seven patients (85 per cent) with T waves deeper than 10 mm This immediately draws attention to the clinical importance of an abnormally deep T wave in the chest lead In three other patients the presence of disease was dubious (cases 3 to 5), and in four others no clear deviation of the heart could be corroborated It is striking that the abnormally deep T wave occurred in forty-three males, whereas our electrocardiographic material represented a few more females than males About 70 per cent of these patients were over 40 years old Bohning and Katz attributed the deep T wave to the symptoms of coronary sclerosis As this deviation of the coronary vessels occurs frequently, it is difficult to say whether electrocardiographic deviations like these must be ascribed to coronary sclerosis or to other additional causes Moreover, the standard leads in our cases did not show the characteristics of coronary sclerosis Over and above that, in many cases of electrocardiographically typical coronary sclerosis we saw no deep T waves in the chest leads^{15a} Nevertheless, we cannot deny the possibility that coronary deviations play a part in the causation of deep

14 Einthoven Arch internat de physiol 4 132, 1906, Arch f d ges Physiol 122 517, 1908

15 Cohn, A E, and Raisbeck, M J Heart 9 311 and 331, 1922

15a An article about changes due to coronary sclerosis will be published by us later

T waves, one can presume that in cases of hypertension chronic nephritis, defects of the aortic valves and arteriosclerotic myodegeneration the coronary vessels are not without defects. On the other hand this explanation is less probable in cases of mitral stenosis (with usually a low tension), mitral insufficiency and exophthalmic goiter.

TABLE 3—Data on the T Waves in Leads I to IV

Sex	Age	Diagnosis	Blood Pressure, mm of Mercury	T ₁ , mm	T ₂ , mm	T ₃ , mm	T ₄ , mm
M	47	Essential hypertension	260/180	—3	—2	1	—11
M	49	Essential hypertension	165/100	3	3	—1	—16
M	62	Essential hypertension	195/100	diph 1	—2	—1	—9
M	67	Essential hypertension	220/110	0	0	0	—16
F	61	Hypertension	175/100	—1	diph 2	3	—13
F	57	Hypertension	200/100	0	1	2	—13
M	58	Hypertension (case 2, section 2)	250/130	2	2	2	—28
M	72	Hypertension	210/110	1	1	0	—18
M	65	Hypertension	235/110	1	1	0	—10
M	62	Hypertension	275/140	2	2	1	—13
M	54	Hypertension, Bright's disease	200/120	diph 2	diph 1	3	—16
M	34	Aortic stenosis	150/ 90	—5	—3	2	—22
M	15	Aortic and mitral regurgitation	155/ 0	—5	diph 2	5	—12
M	47	Aortic regurgitation	170/ 0	0	—3	—2	—15
M	46	Aortic	134/ 58	diph 1	diph 1	0	—15
M	65	Aortic	235/110	1	1	0	—10
M	51	Aortic	180/ 70	2	3	1	—11
M	41	Mitral insufficiency	175/110	—2	diph 1	2	—15
M	58	Mitral insufficiency	135/ 90	5	5	—1	—20
M	64	Mitral insufficiency	145/ 90	—2	3	7	—13
M	34	Mitral insufficiency	125/ 80	4	9	5	—18
M	33	Mitral stenosis	110/ 60	6	7	4	—18
M	55	Mitral stenosis	130/ 70	3	5	2	—12
M	33	Mitral stenosis	125/ 70	4	5	3	—15
M	37	Mitral stenosis	110/ 85	4	5	1	—10
M	21	Mitral insufficiency (case 1, section 2)	120/ 45	0	9	10	—30
M	36	Mitral insufficiency	115/ 70	1	0	0	—12
M	61	Complete heart block	195/ 70	diph 2	6	6	—18
F	64	Bundle branch block	175/100	—7	2	8	—16
M	54	Bundle branch block	150/ 90	—5	—3	2	—22
M	57	Auricular fibrillation	155/100	0	0	2	—13
F	66	Myodegeneration	120/ 55	—2	—2	0	—18
M	52	Myodegeneration	110/ 65	4	3	—1	—12
M	60	Myodegeneration	135/ 75	2	3	3	—12
M	78	Myocarditis	135/ 75	diph 2	4	5	—10
M	63	Coronary sclerosis	140/100	—3	0	3	—13
M	56	Angina pectoris	135/ 90	4	4	1	—14
M	52	Auricular fibrillation	140/ 85	4	0	1	—11
M	72	Auricular fibrillation	130/ 75	1	1	0	—12
M	27	Rheumatic polyarthritis	130/ 85	7	5	diph 1	—15
F	28	Exophthalmic goiter	150/ 0	4	4	2	—13
M	43	No deviations	130/ 65	4	7	5	—13
F	49	Case 4	125/ 75	2	5	2	—14
M	33	Case 3	120/ 75	6	7	2	—14
M	26	Case 5	135/ 85	4	6	4	—13
M	31	No deviations	130/ 80	1	4	3	—13
M	29	No deviations	130/ 70	3	5	3	—15

As a working hypothesis we may assume that in cases of mitral defects revolving of the heart and in some other cases coronary changes play a part. The deep T waves were partly found in bundle branch or auricular fibrillation block, in analogy to the diphasic ventricular complexes in the other leads (fig 7 D). As for the T waves in the other leads (table 3) in twenty-seven cases the T waves in leads I and II were positive (though low in seven), and in the other twenty cases in both lead I and II the T wave was either negative or flat. Positive T waves in the three standard leads were found seventeen times in forty-seven

cases, so in more than one third of all cases lead IV offered the only deviation! This demonstrates the importance of the chest lead for this group as well as for the others. It impressed us that in the four cases of mitral stenosis in which there were deep T waves the T waves in the limb leads were always positive. Now the question arises as to how far this T wave indicates insufficiency of the myocardium. In about one third of the cases there were clinical indications of decompensation (dyspnea, cyanosis, a distinctly more rapid pulse rate, edema and congestion of the lungs), in the other cases these symptoms were absent.

In summarizing our data we may say that the greater part of our patients (85 per cent) who showed a deep T wave in the thoracic electrocardiogram clearly showed signs of organic disease of the heart or of the cardiovascular system, in some cases such diagnoses were plausible, though they could not be proved (5 per cent), and in the other cases (10 per cent) they could not be demonstrated. The deep T wave did not prove to be a sure sign of myocardial insufficiency. The following case reports illustrate these features.

CASE 1 (fig 7 A)—A man aged 21 was suffering from a combined mitral defect. He complained of palpitations, shortness of breath and a heavy feeling in the cardiac region on exertion. These symptoms began six years before his admission to the clinic, after an attack of acute polyarticular rheumatism. On examination a raising impulse was found which extended outside the medioclavicular line, on percussion the heart appeared to be enlarged to the left and to the right, and on auscultation a loud first sound and a soft presystolic and a rough systolic murmur were heard. An electrocardiogram⁹ showed a large ventricular complex in the first lead, right axis deviation and high T waves in leads II and III. In lead IV the T wave was 30 mm deep.

CASE 2 (fig 7 B)—A man aged 58 had a blood pressure of 250 systolic and 130 diastolic. The heart was slightly enlarged to the left, with a somewhat widened aorta. For the rest there were no clear deviations. The diagnosis was arteriosclerotic hypertension and arteriosclerosis of the aorta. An electrocardiogram showed strong left axis deviation. In leads I to III the T wave was low, but in lead IV it was 28 mm deep.

CASE 3 (fig 7 C)—A man aged 33 complained of slight oppression and palpitations on exertion. On physical examination no important deviations from normal were found. The blood pressure was 120 systolic and 75 diastolic. Tests for syphilis were negative. Percussion and auscultation of the heart revealed no abnormality. However, roentgen examination showed that the aorta was wide and that the heart was dilated to the left. We therefore could not consider the heart of this patient to be entirely normal. The only peculiarity shown by the electrocardiogram was that the T wave in lead IV was 14 mm deep.

CASE 4—A woman aged 49 had for some time complained of attacks of palpitation, which occurred about once a fortnight. After such an attack the patient vomited and urinated several times. She was greatly fatigued. On physical examination no deviations were found, except that once there was total irregular tachycardia. Such an attack was not recorded electrocardiographically. The only

peculiarity the electrocardiogram showed was a T wave of -14 mm in lead IV. It is not improbable that this woman suffered from paroxysmal auricular fibrillation. Therefore, it is possible, though it cannot be proved, that the depth of T₄ here implied a pathologic condition.

CASE 5—A man aged 26 complained of having sometimes a gripping feeling in the chest, together with vomiting. This had nothing to do with exertion, eating or emotion. Otherwise the patient was in good health. The blood pressure was normal. The heart showed no peculiarities either on the roentgenogram or on

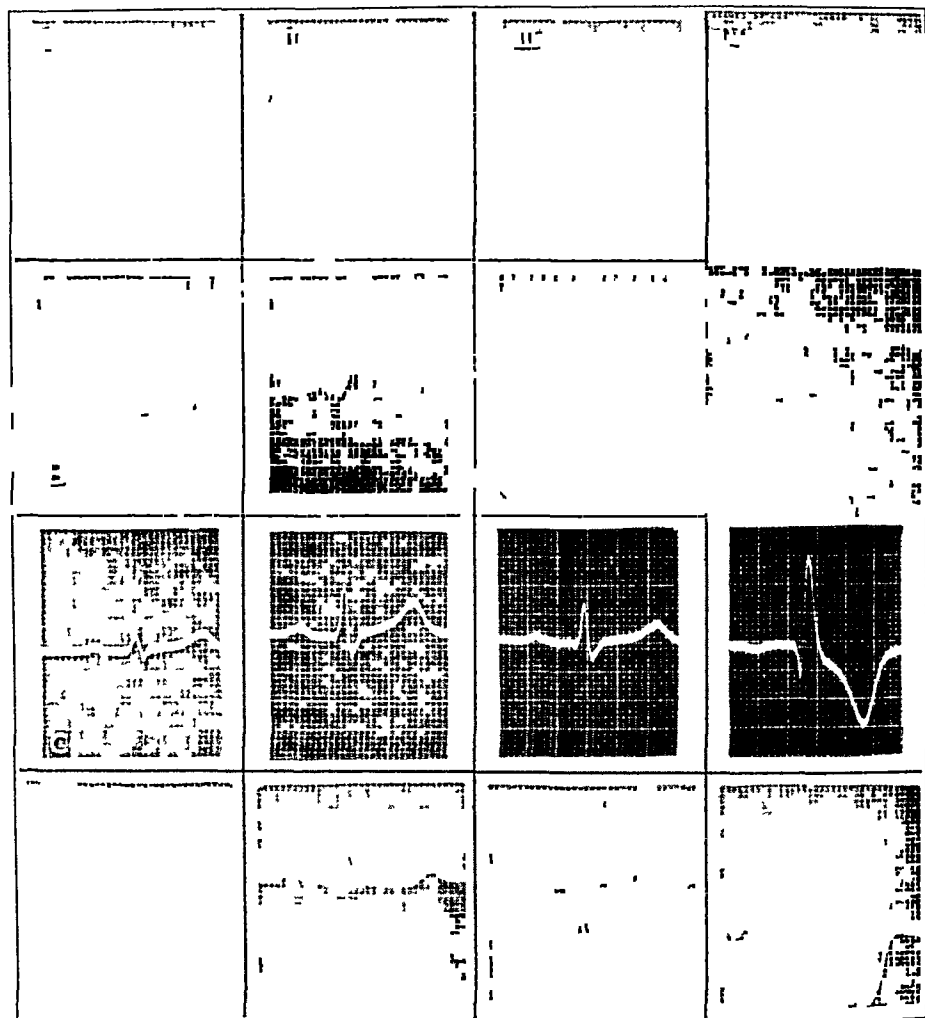


Fig 7—Examples of deep T waves. A (case 1, section 2) shows a deep T wave in mitral stenosis. B (case 2, section 2) shows a deep T wave in arteriosclerotic hypertension. For data on C see case 3, section 2. D shows a deep, broad T wave in bundle branch block.

physical examination. The urine contained some albumin, erythrocytes and granular casts. The only peculiarity the electrocardiogram showed was a T wave of -13 mm in lead IV. Does such an electrocardiographic picture offer the starting point for making a diagnosis of disease of the heart? For the present we do not believe that it does.

3 THE FLAT AND INVERTED T WAVE

Not only in cases of myocardial infarction due to coronary thrombosis but also in cases of damage to the myocardium due to other causes the chest lead may be of diagnostic value. Wood and Wolferth and their co-workers^{2c} have already pointed this out. Hoffman and Delong¹² were the first to study the deviations of the T wave in lead IV in some cases of myodegeneration and other diseases of the myocardium. However, they came to the conclusion that the standard leads as a

TABLE 4—Data on the T Waves in Leads III and IV

Sex	Age	Diagnosis	T ₃	T ₄
F	32	Hypertension, diabetes	—	+
M	66	Hypertension, diabetes	—	+
F	52	Hypertension, angina pectoris	—	Trace
F	55	Hypertension	—	+
F	36	Hypertension	—	Shallow
F	61	Hypertension, angina pectoris	—	+
F	61	Hypertension	—	Shallow
F	41	Hypertension	Trace	Shallow
F	40	Hypertension (hypertrophied)	—	Shallow
F	44	Hypertension	Trace	Trace
F	50	Hypertension	—	+
F	44	Hypertension	—	Diphasic
F	40	Hypertension	Flat	Flat
F	9	Hypertension	—	Flat
F	47	Angina pectoris	+	+
F	36	Angina pectoris	—	+
F	44	Angina pectoris	—	Diphasic
F	46	Angina pectoris	—	+
F	35	Anginous syndrome	Diphasic	Diphasic
F	45	Coronary sclerosis	—	—
F	45	Coronary sclerosis, diabetes	—	Flat
F	50	Myodegeneration	Flat	+
F	26	Heart failure	—	Shallow
F	30	Aortic regurgitation	—	Diphasic
F	53	Syphilitic aortitis	Flat	Shallow
F	41	Mitral stenosis	Diphasic	Diphasic
F	22	Auricular extrasystoles	Flat	+
F	36	Extrasystoles, heart failure	Flat	Shallow
M	7	Ventricular extrasystoles	Diphasic	Shallow
F	20	Ventricular extrasystoles	—	Shallow
F	14	Ventricular extrasystoles	—	Diphasic
F	9	Ventricular extrasystoles	Diphasic	+
F	41	Exophthalmic goiter	—	+
F	39	Exophthalmic goiter	—	Shallow
F	35	Simple goiter	—	Shallow
F	16	Simple goiter, tachycardia	Diphasic	Shallow
M	5	Diphtheria, nephrosis	Diphasic	+
F	7	Diphtheria	—	Diphasic

rule offer sufficient data about the condition of the myocardium. Bohning and Katz^{4e} favored the same opinion, and of late Scherf¹⁴ has once more defended this view. Korth and Hecht,¹⁶ on the other hand, published examples which illustrated the importance of the chest lead in diffuse myocardial lesions, when the limb leads answer this question either insufficiently or not at all. One of us (van Nieuwenhuizen^{4a}) described some cases of rheumatic myocarditis in which plain deviations were seen only in lead IV, whereas in some cases the picture of the T wave in the fourth lead changed analogically with the condition of the patient.

In our first group of fifteen hundred electrocardiograms with four leads we found deviations of the T wave in the chest lead (except those mentioned in sections 1 and 2) in one hundred and fifty-five cases. In forty-six of them the T wave in leads I and II was either low or flat or negative. As the chest leads in this group did not settle the diagnosis, these cases will be left out of consideration. Forty-four of the other one hundred and nine electrocardiograms showed a flat, low or negative T wave in the third lead (table 4). In this group the chest lead (with a restriction to be mentioned later) as a rule settled the question of judging the condition of the myocardium. In the remaining sixty-five electrocardiograms only the fourth lead deviated from the standard (table 5). These figures show that the chest lead does not correspond exactly with the standard leads. The desirability of bringing the electrocardiographic method to perfection when diagnosing diffuse myocardial damages will be appreciated by every one who is familiar with those frequent cases in which there are obvious clinical symptoms of cardiac failure but the limb leads do not show typical changes. However, when the T wave in the fourth lead is being judged some factors must be considered. It is agreed that digitalis influences the shape of the T wave just as much in the chest lead as in the standard leads (Strauss,¹⁷ van Nieuwenhuizen¹⁸). Also, just as in limb leads heating or cooling the surface of the chest above the cardiac apex may cause an inversion of the T wave (Jervell¹⁸). Finally, it impressed us that sometimes a positive T wave was found in the anteroposterior or the anterior left leg lead in clinically healthy subjects, especially children. On closer examination we found that these patients had a "dropping heart," or a long, steep heart, of which the low R wave in lead I and high R waves in leads II and III were mostly, but not always the expression in the limb leads. Also as a rule the T wave was low in lead I and high in lead II. When interpreting the thoracic electrocardiogram it is important to remember this fact and not to consider an inverted T wave in lead IV in patients with long, steep hearts and in children as a symptom of myocardial disease. Recently Graybiel and White¹⁹ described a negative T wave in the standard leads in fairly normal subjects. However, an examination of their case reports shows that some of the patients suffered from paroxysmal tachycardia and thyrotoxicosis. Aside from these less convincing cases, there were some in which a diagnosis of "neuro-circulatory asthenia" had to be made. Of course it cannot be denied that a gradually intruding infection may have developed, but that would

17 Strauss, H., and Katz, L. N. *Am Heart J* **10** 546, 1935

18 Jervell, A. *Acta med Scandinav*, supp 68, 1935, p 1

19 Graybiel, A., and White, P. D. *Am Heart J* **10** 345, 1935

stamp the electrocardiographic and clinical diagnoses *ad absurdum*. It must not be forgotten that Lewis found the T wave minimally to be -0.5 mm in lead I in normal subjects, and in lead II there was sometimes a "trace." Possibly our cases of inverted T waves in

TABLE 5—Further Data on the T Waves in Leads III and IV

Case	Sex	Age, Years	Diagnosis	T ₃	T ₄
1	F	39	Hypertension	+	Diphasic
2	F	53	Hypertension	+	+
3	M	75	Hypertension	+	Shallow
4	F	59	Hypertension	Flat	Flat
5	F	31	Hypertension	Flat	Shallow
6	F	61	Hypertension	+	+
7	F	45	Hypertension	Flat	Shallow
8	F	14	Hypertension, Bright's disease	+	+
9	F	56	Hypertension, diabetes	+	+
10	M	42	Hypertension, angina pectoris	+	+ High
11	F	47	Hypertension, angina pectoris	+	+
12	F	32	Angina pectoris	Diphasic	+
13	F	59	Angina pectoris	Flat	Shallow
14	F	43	Angina pectoris	Flat	Shallow
15	F	50	Coronary sclerosis	Flat	Flat
16	M	51	Coronary sclerosis, heart dilated	+	+
17	F	57	Coronary sclerosis	+	Shallow
18	F	50	Coronary sclerosis	+	Shallow
19	M	45	Coronary sclerosis, emphysema	—	Shallow
20	M	61	Coronary sclerosis, diabetes	Flat	Shallow
21	F	41	Numerous extrasystoles	+	+
22	F	1½	Numerous extrasystoles following diphtheria	+	+
23	F	36	Numerous extrasystoles, escaped beats	+	Shallow
24	M	41	Nervous tachycardia	Flat	Shallow
25	F	18	Nervous tachycardia	+	Shallow
26	F	55	Palpitations	+	Shallow
27	F	31	Paroxysmal tachycardia (?)	+	Diph
28	F	58	Exophthalmic goiter	+	Diph
29	F	11	Exophthalmic goiter	+	+
30	F	14	Exophthalmic goiter	Flat	Shallow
31	F	21	Exophthalmic goiter	+	Diph
32	F	27	Exophthalmic goiter	+	+
33	F	38	Exophthalmic goiter	—	+
34	F	21	Mitral stenosis	Flat	+
35	F	48	Mitral stenosis	—	Shallow
36	F	20	Mitral stenosis	—	+
37	F	42	Mitral stenosis	+	Shallow
38	F	56	Mitral stenosis insufficiency	Flat	+
39	F	29	Mitral insufficiency	+	Shallow
40	M	57	Mitral insufficiency	+	Diph
41	F	24	Mitral insufficiency	+	Shallow
42	M	43	Aortic regurgitation	+	+
43	M	10	Postrheumatic complicated defect	+	+
44	M	12	Endocarditis	+	+
45	M	7	Sydenham's chorea	Flat	+
46	M	2½	Congenital malformation	+	+
47	M	15	Congenital malformation	+	Shallow
48	F	36	Aneurysm of subclavian artery	Flat	+
49	F	2	Bronchopneumonia	+	+
50	F	30	"	Flat	Shallow
51	M	12	"	+	+
52	F	35	"	+	Shallow
53	F	37	Hysteria	+	+
54	M	38	Tumor of spinal cord	+	+
55	F	19	Neurotic complaints	+	Shallow
56	M	15	Syncope without known origin	+	Shallow
57	F	16	Pains in back	+	+
58	F	34	Cholelithiasis	+	Flat

fairly normal persons are analogous to those of White (in which the cause was not known), but to us it seems more probable that the position of the heart was the causal factor.

CASE 1 (table 5, case 33, fig 8 A)—A woman aged 38 suffered from hyperthyroidism. She had distinct tremors of the hands and a pulse rate of 104. The

blood pressure was 200 systolic. The basal metabolism was +61 per cent. A roentgenogram showed the heart to be dilated to the left, possibly with dilation of the right ventricle. An electrocardiogram showed no distinct deviations in leads I and II, in lead III the T wave was low but positive in the anteroposterior lead. So here the chest lead offered the only electrocardiographic sign that this severe hyperthrosis was combined with disease of the myocardium.

CASE 2 (table 5, case 40, fig 8 B) —A workman aged 57 suffered from stomach trouble and palpitations. Sometimes he awoke with an intense pain in the cardiac region. The blood pressure was 100 systolic and 75 diastolic. There was slight peripheral arteriosclerosis. On percussion and roentgenographically the heart appeared to be enlarged. Above the mitral valve a systolic murmur was heard. The diagnosis was mitral insufficiency. The liver was slightly enlarged. An electrocardiogram showed low ventricular complexes in lead I, the course of the ST segment was aniso-electrical and saddle shaped. In lead II there were small ventricular complexes with a notch in S. In lead III the course of ST was aniso-

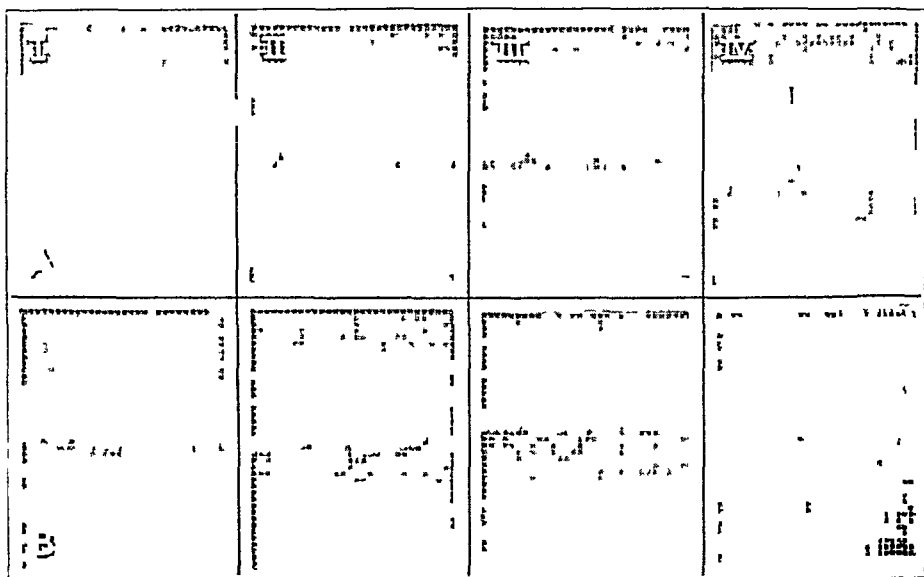


Fig 8—Examples of diphasic and positive T waves following diffuse injury to the myocardium. For data on A see case 1, section 3, and for B see case 2, section 3.

electrical, here too the ventricular complexes were small. In all three leads the T waves were positive. In lead IV the T wave was diphasic. With the other deviations these findings indicated a none too favorable condition of the myocardium. It is a question whether here there was not a C 2 type of tracing, which then indicated the pressure of anterior infarction which had arisen chronically.

SUMMARY

Data obtained from the chest lead derived as a routine method are discussed on a basis of fifteen hundred tracings. In coronary thrombosis the chest lead often offers the only electrocardiographic diagnostic evidence. The importance of the chest lead for the differential diagnosis of acute intrathoracic or abdominal deviations with coronary

thrombosis is pointed out. The chest lead may be of much value also in reaching a diagnosis in a case of gradually arising myocardial infarction. The tracings obtained in coronary thrombosis are divided into two groups, one of which (C2 type, fig 1 *B* and *C*) was caused by anterior infarction and the other (C1 type, fig 1 *D* and *E*) possibly by posterior or septal infarction.

It is not improbable that these last curves indicated an atypical bundle branch block. But there still remains the question whether the cause is not an insufficiency of the blood supply by the posterior coronary artery.

The latter form of tracing (C1) was seen in one case of rheumatic myocarditis. The history of a patient in the first group usually records an acute attack, that of a patient in the second group usually bears no record of a sudden attack of pain or oppression. This is the reason these myocardial changes often escape clinical observation. Next the clinical significance of an abnormally deep T wave (deeper than —10 mm) is pointed out. With a few exceptions such a wave is always found in organic disease of the heart. In cases of mitral stenosis, however, the T waves in the standard leads are strongly positive, in other groups (hypertension, chronic nephritis and aortic defects) all or part of them are abnormal. The hypothesis is advanced that the deep T wave in mitral stenosis is the result of a difference in the position of the heart; in the other groups this might be the result of myocardial disease. A deep T wave is found also in bundle branch block. Then, however, the ventricular complex is very high and large, in analogy to the diphasic ventricular complexes in the other leads.

Finally the importance of the chest lead in making an electrocardiographic diagnosis of diffuse myocardial damage is demonstrated either as a support for the third lead (table 4) or as the sole criterion (table 5). Here the T wave may be shallow, diphasic or positive. Other factors which influence the shape of the T wave in the chest lead are digitalis and a longitudinal position of the heart, especially in children.

ANATOMIC FEATURES OF THE CARDIAC ORIFICE OF THE STOMACH

WITH SPECIAL REFERENCE TO CARDIOSPASM

FREDERICK C LENDRUM,* M.D., PH.D.

DETROIT

The clinical problems which concern the lower end of the esophagus and the cardiac orifice of the stomach are basically anatomic problems. The occurrence and nature of esophageal varices depend on the venous supply and the anastomoses across the cardia, as has been demonstrated by Kegaries¹. The study of peptic ulcer of the esophagus raises the question of the competence of the sphincteric action of the cardia in preventing the regurgitation of gastric juice and also the question of the occurrence of islands of gastric mucosa in the esophagus. Carcinoma of the cardia and the lower extremity of the esophagus also is of extreme anatomic interest. The peculiar glandular epithelium which is present at the cardia might be expected to give rise to neoplasms which have different properties from those of neoplasms which originate elsewhere in the stomach and esophagus. Moreover, the metastasis of a carcinoma at the cardia depends on the distribution of the lymphatic glands in this region, which has been much less satisfactorily studied than has the lymphatic drainage of the stomach. Finally, the phenomenon of cardiospasm which is the most important clinical condition associated with this region, doubtless depends for its explanation on some peculiarity of the musculature, nerve supply or external pressure at this point in the enteric canal.

Much labor has been spent on the study of the anatomic features of the stomach, and no small amount of attention has been directed also to the esophagus. Surprisingly little thought, however, has been given to the point of transition between these two organs. Accordingly, for the most part there are no adequate descriptions of what happens to the various tissues as they pass from the esophagus into the stomach. For the purposes of the present paper the word cardia will be used to cover this region of transition, including the lower extremity of the esophagus,

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1 Kegaries, D. L. The Venous Plexus of the Esophagus. Its Pathological and Clinical Significance, Thesis, University of Minnesota Medical School, 1932

the point of juncture with the stomach and the adjacent portions of the stomach. If the term *cardia* should sound to the literary purist like a colloquial modern abbreviation for "cardiac orifice," it may console him to know that this word was used in the "Commentaries" of Heberden² as early as 1802.

GENERAL DESCRIPTION OF THE CARDIAC ORIFICE

After passing through the diaphragm the lower end of the esophagus curves to the left and enters the inner aspect of the upper end of the stomach at the cardiac orifice. In the human adult the abdominal portion of the esophagus, which is termed the cardiac antium, is about 2 cm in length. At the cardiac orifice the right margin of the esophagus is continuous with the lesser curvature of the stomach, while the left margin joins the greater curvature at an acute angle, which is termed the *incisura cardiaca*. This angulation is dependent on the form and position of the adjoining fundus.

When the esophagus and stomach are opened at necropsy, the mucous membrane at the *cardia* presents an abrupt change in appearance from the smooth, white, opaque, parchment-like mucous membrane of the esophagus and the mamillated pink mucus-covered lining of the stomach. This contrast more often than not is partially effaced by postmortem erosion around the *cardia*.

The esophageal epithelium terminates not in a straight but in a jagged, irregular and angulated line. Just below this line in the adult there is a groove, which is formed by the orifices of the cardiac glands, which in the adult undermine the lower end of the esophageal epithelium. Microscopically the epithelium of the esophagus is observed to be, in the human species, of a thick noncornified stratified squamous variety, with numerous papillae, arranged linearly in the axis of the esophagus (fig 1). At the *cardia* the stratified squamous epithelium of the esophagus changes abruptly to the simple columnar epithelium of the stomach (fig 2). Beneath both varieties of epithelium, at intervals of about 2 or 3 mm in the ordinary section, are the mucosal lymph follicles. Likewise, beneath both varieties of epithelium are the cardiac glands. In the human infant, as well as in eight other species of mammals which I have examined, the cardiac glands have the structure of stunted or incomplete fundic glands. Bensley,³ who has

2 Heberden, William. Commentaries on the History and Cure of Diseases, London, T. Payne, 1802.

3 Bensley, R. R. The Cardiac Glands of Mammals, *Am J Anat* 2: 105-156 (Nov. 29) 1902, The Cardiac Glands of the Mammalian Stomach, *Anat Rec* 4: 375-390, 1910, The Gastric Glands, in Cowdry, E. V. Special Cytology. The Form and Function of the Cell in Health and Disease, New York, Paul B. Hoeber, Inc., 1928, vol. 1, pp. 139-167.

investigated the cardiac glands in much detail, concluded that they are essentially fundic glands the development of which has been in some way inhibited. This inhibitory influence is apparently lost in middle adult life, when the cardiac glands undergo an adenomatous hyperplasia which produces bizarre irregular masses of glandular tissue.

The cardia is the site of striking changes in the subepithelial connective tissue, which take place by gradations over the region occupied by the cardiac glands. In the esophagus there is a fairly thick layer of connective tissue and lymph follicles between the epithelium and the muscularis mucosae. This layer is more cellular and much more dense than the submucosal layer, which it approaches in thickness. It con-

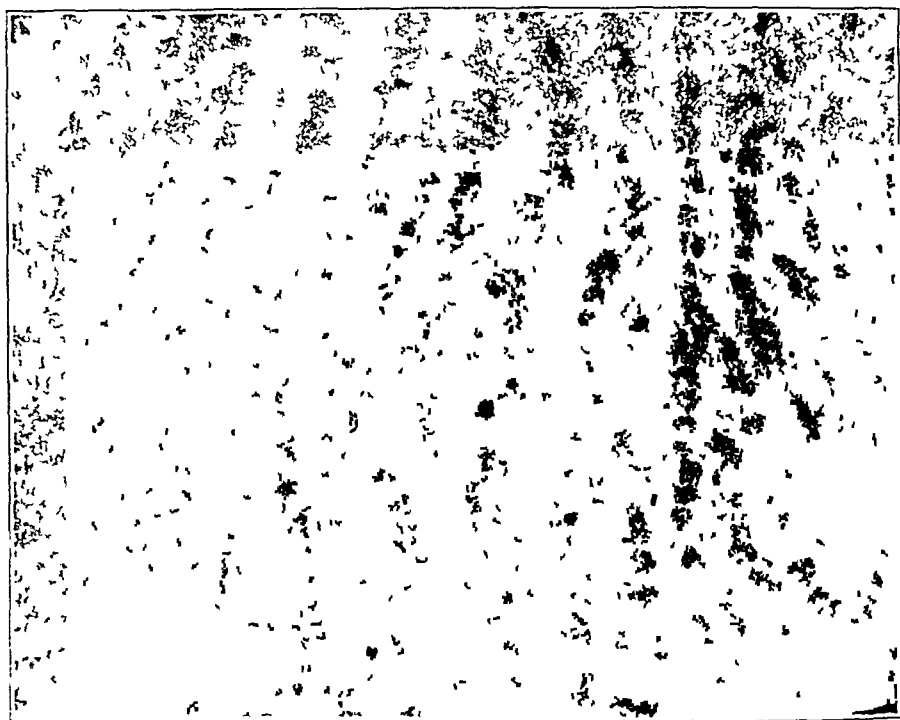


Fig. 1—Full thickness section of the esophageal mucosa at the cardia, cleared to show the linear longitudinal arrangement of the papillae ($\times 28$)

tains no fat cells. The lamina of subepithelial connective tissue continues unchanged to the lower border of the esophageal epithelium. In the region of the cardiac glands this layer is invaded and distorted by irregular masses of glandular tissue. When the true fundic glands are reached, the muscularis mucosae is applied directly to the fundic ends of the glands, and the mucosal layer of connective tissue almost disappears.

No less dramatic are the changes which take place in the muscularis mucosae. Throughout the esophagus the muscularis mucosae is very thick, in fact it is possible to find sections in which it equals in thick-

ness that of the outer longitudinal layer of the muscularis propria. The muscularis mucosae has no sheath. It does not form even a single dense lamina but is made up of ragged longitudinal strands of smooth muscle separated by connective tissue. In the small intestine the muscularis mucosae is made up of an inner circular and an outer longitudinal layer. In the larger part of the stomach it is made up of three layers. However, in the esophagus, at the cardia and in the neighboring few centimeters of the stomach I have never seen anything except longitudinal fibers in the muscularis mucosae. The muscularis is unchanged throughout the esophagus as far as the cardia. The cardiac glands in

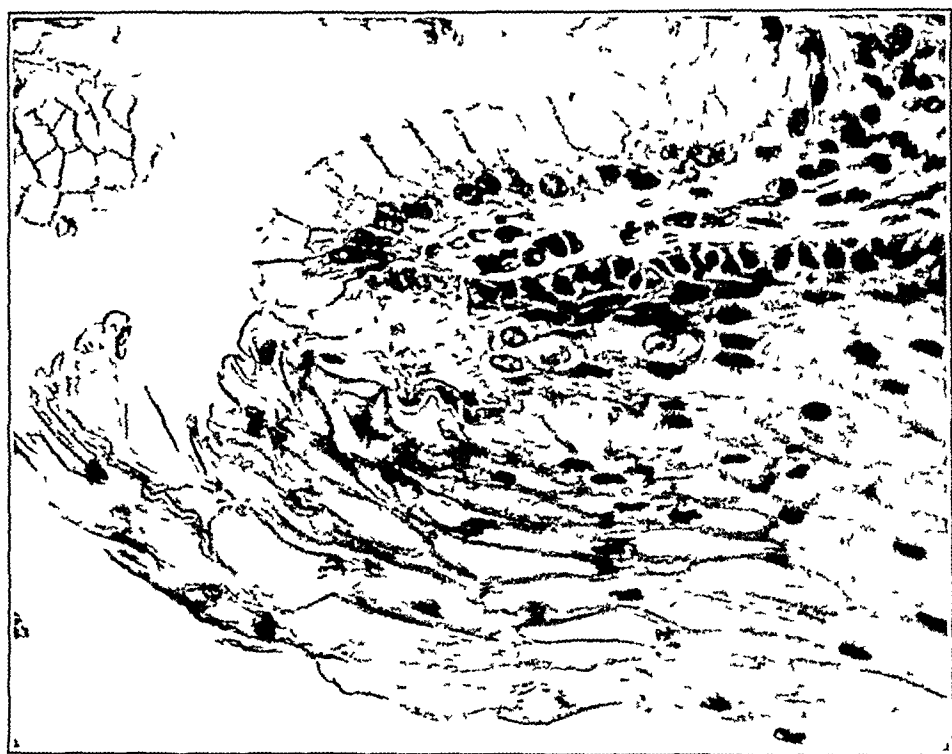


Fig 2—Point of juncture between the squamous and the columnar epithelium at the cardia ($\times 340$)

the adult sometimes break into the muscularis, so that while these glands lie mostly superficial to the muscularis, strands of muscular tissue may surround the deep layers of the cardiac glands. As soon as the muscularis mucosae reaches the region of the fundic glands, which is generally within 1 or 2 cm of the end of the esophageal epithelium, it becomes a much thinner but more dense and regular layer and is applied closely to the ends of the glands.

The submucous layer of the esophagus is composed of acellular loose connective tissue. The submucosal layer contains the esophageal glands proper, which are closely applied to the outer surface of the muscularis mucosae. It contains also a few scattered fat cells. As the submucous layer passes down the esophagus and into the stomach, it

gradually becomes more dense, but there is no sudden change or break at the cardia. The submucosa contains many more and larger vessels than are present in the mucosa. It contains also Meissner's submucous plexus, the strands of which are sparse and greatly attenuated in the region of the cardia and are difficult to demonstrate. I have never seen ganglion cells in the submucous plexus of the human esophagus. Greving⁴ also failed to find them, and Koslowski⁵ apparently demonstrated that they do not occur in the submucous plexus of the esophagus of the cat or rabbit.

External to the submucosa is the circular muscle, arranged in bundles, with an inner and an outer sheath of connective tissue. Outside this lies the intermuscular septum, which contains the myenteric (Auerbach) plexus, in addition to a network of blood vessels. In the esophagus the intermuscular septum is a thick layer of connective tissue, and the same is true for the cardia. In the middle of the lesser curvature of the stomach, however, the intermuscular septum is greatly thinned, and when the small intestine is reached, there is no longer any intermuscular septum, and the ganglions of the myenteric plexus lie naked between the two muscular layers.

External to the intermuscular septum lies the longitudinal muscle. This muscle is ordinarily about half the thickness of the circular muscle and like it is arranged in bundles. These bundles are densely packed in the adult, but in the new-born infant the bundles may be sufficiently separated so that single longitudinal sections may give the impression of "breaks" in the longitudinal muscle. In the stomach below the cardia the layer of longitudinal muscle gradually becomes thinner.

In the human being the muscle at the cardia is all smooth muscle. Though occasional instances have been described in which striated muscle fibers have extended down this far (as by Arey and Tremaine⁶), I have never seen anything but smooth muscle in the region of the cardia. In the adventitia, of course, strands of striated muscle, which extend from the diaphragm, are frequently present.

The adventitia in the region of the cardia contains much loose acellular connective tissue, with coarse longitudinal elastic fibers and large nerve trunks. The larger blood and lymph vessels course in this layer.

MUSCULARIS PROPRIA

Because of the vast practical importance of the clinical phenomenon of cardiospasm, the anatomic aspect of the cardia which arouses most

⁴ Greving, R., quoted by Kuntz³⁴

⁵ Koslowski, quoted by Kuntz³⁴

⁶ Arey, L. B., and Tremaine, M. J. The Muscle Content of the Lower Esophagus of Man, *Anat. Rec.* **56** 315-320 (July 25) 1933

general interest is the question of a sphincter muscle in this situation, for it is by no means established that the condition which may be termed idiopathic dilatation of the esophagus is actually the result of spasm at the cardia. Spasm of the diaphragm, pressure by the liver, pressure by the "tips" of the lungs, paralysis of the esophagus, failure of the reflex relaxation of the cardia, fibrosis of the terminal portion of the esophagus and torsion of the esophagus are other causes which are used to explain this malady. Even the site of obstruction in cardiospasm is not agreed on. Carman⁷ said that it is generally at the diaphragmatic orifice, while Alvarez asserted that it is 2 cm lower, at the cardia.

Some enlightenment on this confusion of theories might be expected if a satisfactory answer could be obtained to the question whether or not the cardia has a sphincter to "go into spasm." This might seem to be the simplest of straightforward anatomic problems, but the investigators are hopelessly at odds about it. Hurst,⁸ Thieding,⁹ Schreiber,¹⁰ Bennett,¹¹ Cannon¹² and Todd¹³ asserted that there is an anatomic sphincter at the cardia. Zaaier,¹⁴ Fleiner,¹⁵ Jackson¹⁶ and Plenk¹⁷ denied the existence of such a sphincter. Abel¹⁸ asserted that there is a sphincter but said that the sphincter is not at the cardia but 1 inch above, at the diaphragmatic orifice. Mosher at one time asserted that the sphincter is "a definite and satisfying structure" and at a later date stated that it does not exist, and this *sic et non* could be continued almost indefinitely.

7 Carman, R. D. *The Roentgen Diagnosis of Diseases of the Alimentary Canal*, ed 2, Philadelphia, W. B. Saunders Company, 1920.

8 Hurst, A. F. Les sphincters du canal alimentaire et leur signification clinique, *Arch. d. mal. de l'app. digestif* **15** 1-34 (Jan.) 1925.

9 Thieding, Friedrich. Ueber Cardiospasmus, Atonie und "idiopathische" Dilatation der Speiseröhre, *Beitr. z. klin. Chir.* **121** 237-300, 1921.

10 Schreiber, quoted by Sturtevant.⁴⁴

11 Bennett, T. I. *The Stomach and Upper Alimentary Canal in Health and Disease*, London, William Heinemann, 1925.

12 Cannon, W. B. *The Mechanical Factors of Digestion*, London, Edward Arnold & Co., 1911.

13 Todd, T. W. *The Clinical Anatomy of the Gastro-Intestinal Tract*, London, Longmans, Green & Co., 1915.

14 Zaaier, J. H. Cardiospasm in the Aged, *Ann. Surg.* **77** 615-617 (May) 1923.

15 Fleiner, W. Neue Beiträge zur Pathologie der Speiseröhre, *München med. Wchnschr.* **47** 529-531 (April 17) 1900.

16 Jackson, Chevalier. *Bronchoscopy and Esophagoscopy*, ed 2, Philadelphia, W. B. Saunders Company, 1927.

17 Plenk, H. Der Magen, in Mollendorff, Wilhelm. *Handbuch der mikroskopischen Anatomie des Menschen*, Berlin, Julius Springer, 1927, vol. 5, pt. 2, pp. 1-234.

18 Abel, A. L. *Oesophageal Obstruction: Its Pathology, Diagnosis and Treatment*, London, Humphrey Mulford, 1929.

On analysis however, this conflict of opinion is not as disturbing as might be expected. The proponents of the sphincter in general (Abel,¹⁸ Mosher,¹⁹ and Huist, for example) did not attempt to defend their opinions with minute dissections or serial reconstructions. They were content to present the photographs of one or two specimens of stomach and esophagus which showed a puckering and muscular thickening at the point of juncture. Abel,¹⁸ in particular said that the sphincter can be satisfactorily demonstrated only by the injection of from 6 to 8 quarts (6 to 8 liters) of solution of formaldehyde into the arteries immediately after death. The error of this method will be apparent at once to any one familiar with the appearance of embalmed organs. In subjects embalmed soon after death there frequently are rings of constriction and muscular thickening every few feet along the whole length of the gastro-intestinal tract. According to the anatomic technic under consideration, the points at which the intestine was fixed in a state of contraction must all be interpreted as sphincters.

The question of a physiologic sphincter at the cardia is not of concern here. There are three morphologic details, however, which may be expected if an anatomic sphincter exists at the cardia: first, a distinct band of circular muscle marked off from the adjoining muscle by connective tissue septums, second, an associated dilator muscle formed by the dipping into the circular muscle of longitudinal fibers, and, third, a local thickening of the circular muscle which persists after the factor of local spasm has been eliminated.

More than one hundred and fifty human cardias were examined microscopically with multiple sections and stains. These specimens covered the whole range from fetal life to advanced senility. In none of the specimens was there seen any special band of circular muscle separated by partitions of connective tissue. In contrast to what Horton observed at the pylorus, both circular and longitudinal muscles appear to be absolutely continuous from the esophagus into the stomach. The circular muscular fibers, it is true, are arranged in anastomosing bundles with connective tissue septums, which is the usual structure in the human gastro-intestinal canal. No septum at the cardia, however, is any larger or more clearly defined than are the others.

Dilator muscles are so generally seen in association with sphincters that the presence of a dilator muscle may be regarded as evidence in favor of the existence of a sphincter. At the pylorus, for example, as Horton²⁰ and others have demonstrated, many of the longitudinal fibers

19 Mosher, H. P. The Lower End of the Oesophagus at Birth and in the Adult, *J. Laryng. & Otol.* **45** 161-180 (March) 1930.

20 Horton, B. T. Pyloric Musculature with Special Reference to the Pyloric Block, Thesis, University of Minnesota Medical School, 1928.

dip in and become buried in the circular muscle to form a dilator of the pyloric canal. In none of the specimens examined was this observed at the cardia. It must be mentioned, however, that in many fetal cardias small isolated strands of smooth muscle from the longitudinal layer were observed to curve in and to be inserted on the connective tissue septum of the inner circular layer. Serial sections revealed that these microscopic pictures represented only aberrant filaments and were not part of a cuff of dilator fibers which extends around the cardia.

In general, the cardias which I examined at necropsy did not reveal any localized muscular thickening. Occasionally, however, particularly in embalmed specimens, the cardia was observed to be puckered and in a state of contraction, and a diffuse ring of thickened muscle was noted at the orifice of the stomach or at the level of the diaphragm or sometimes involving both sites. In order to eliminate the factor of spasm, five fresh unopened specimens of cardia were fixed in solution of formaldehyde with a small test tube inserted through the cardiac orifice and into the lower part of the esophagus to produce uniform dilatation. These specimens were then opened anteriorly and examined both grossly and by microscopic sections obtained from the anterior and posterior surfaces and from the right and left sides of the cardiac orifice. In no case was there any localized muscular thickening which resembled a sphincter muscle.

I am forced to conclude, therefore, that in the human being there is no morphologic evidence of a sphincter muscle at the cardia. Moreover, the evidence from comparative anatomy would not lead one to expect an anatomic sphincter at this point. Gross and microscopic examinations were made of the juncture of the esophagus and stomach of the fish, salamander, frog, snake, pigeon, hog, calf, rat, mouse, rabbit, guinea-pig, dog, cat and monkey. Only in the group of rodents was localized muscular thickening noted which might be looked on as a cardiac sphincter. In the rat, mouse and guinea-pig this was associated with a reduplication of the mucosa, which apparently functions as a valve to prevent regurgitation from the stomach.

Despite the absence of a sphincter, there is one respect in which the circular fibers at the cardia differ from those in the remainder of the esophagus. This concerns the relationship of the circular fibers to the oblique muscle of the stomach.

In order to reveal by dissection the full extent of the oblique muscle, five unopened specimens of stomach and esophagus were turned inside out. The mucosa was stripped from the surface, and the submucous connective tissue was completely removed by dissection, which exposed the oblique muscle.

The oblique muscle is to be regarded as a special group of inner fibers of the circular muscle of the stomach. It does not form a com-

plete layer in the stomach. On the contrary, it is a U-shaped band, the curve of the U being the loop which passes over the cardiac incisura and the arms of the U being two strands which extend down the lesser curvature on either side of the magenstrasse. The dissections revealed that the oblique fibers loop up into the esophagus for as much as 1 cm and blend with the circular muscle on the left aspect of the cardia (fig 3 A). At this point the circular and oblique muscles have approximately the same direction and merge sufficiently so that they usually are not readily distinguished in microscopic sections. M'Swiney²¹ has observed the same picture in lower animals. What practical significance these facts may have I cannot say. The possibility, however, that overaction of the oblique muscle may exert a pinchcock action on the cardiac orifice seems deserving of consideration in connection with the study of cardiospasm.

THE ELASTIC TISSUE OF THE CARDIA

The elastic tissue of the human esophagus has been carefully described by Schumacher²². He did not consider, however, the question of what modifications take place at the cardia. The arrangement of the elastic tissue in the stomach has been summarized by Plenk¹⁷ largely from the studies of Schutz²³. The work of Schutz on the elastic tissue of the stomach is regarded as the most authoritative, although Schutz based his conclusions on a study of only two stomachs. Schutz seems to have been the only writer to give much attention to the question of the variations in the elastic tissue of different parts of the stomach. He said that in the region of the pylorus the submucosa is richer in elastic fibers than it is elsewhere while in the region of the cardia there is an increase in the elastic tissue in the sheaths of the muscularis propria. His expression *Cardia region*, however, is not sufficiently definite to answer the question of what happens at the cardiac orifice.

The work of Mosher and McGregor²⁴ in 1928 reopened the question of the arrangement of the elastic tissue around the cardia and raised the question of its clinical significance. These authors said that

21 M'Swiney, B. A. The Structure and Movements of the Cardia, *Quart J Exper Physiol* **19** 237-241, 1929.

22 Schumacher, S. Die Speiseröhre, in Mollendorff, W. *Handbuch der mikroskopischen Anatomie des Menschen*, Berlin, Julius Springer, 1927, vol 5, pt 1, pp 301-336.

23 Schutz, Emil. Zur Kenntnis des elastischen Gewebes des Magens, *Arch f Verdauungskr* **13** 49-58, 1907, *Beiträge zur Histologie des menschlichen Magens*, *ibid* **14** 241-250, 1908.

24 Mosher, H. P., and McGregor, G. W. (a) A Study of the Lower End of the Esophagus, *Tr Am Laryng, Rhin & Otol Soc* **34** 294-340, 1928, (b) A Study of the Lower End of the Esophagus, *Ann Otol, Rhin & Laryng* **37** 12-70 (March) 1928.

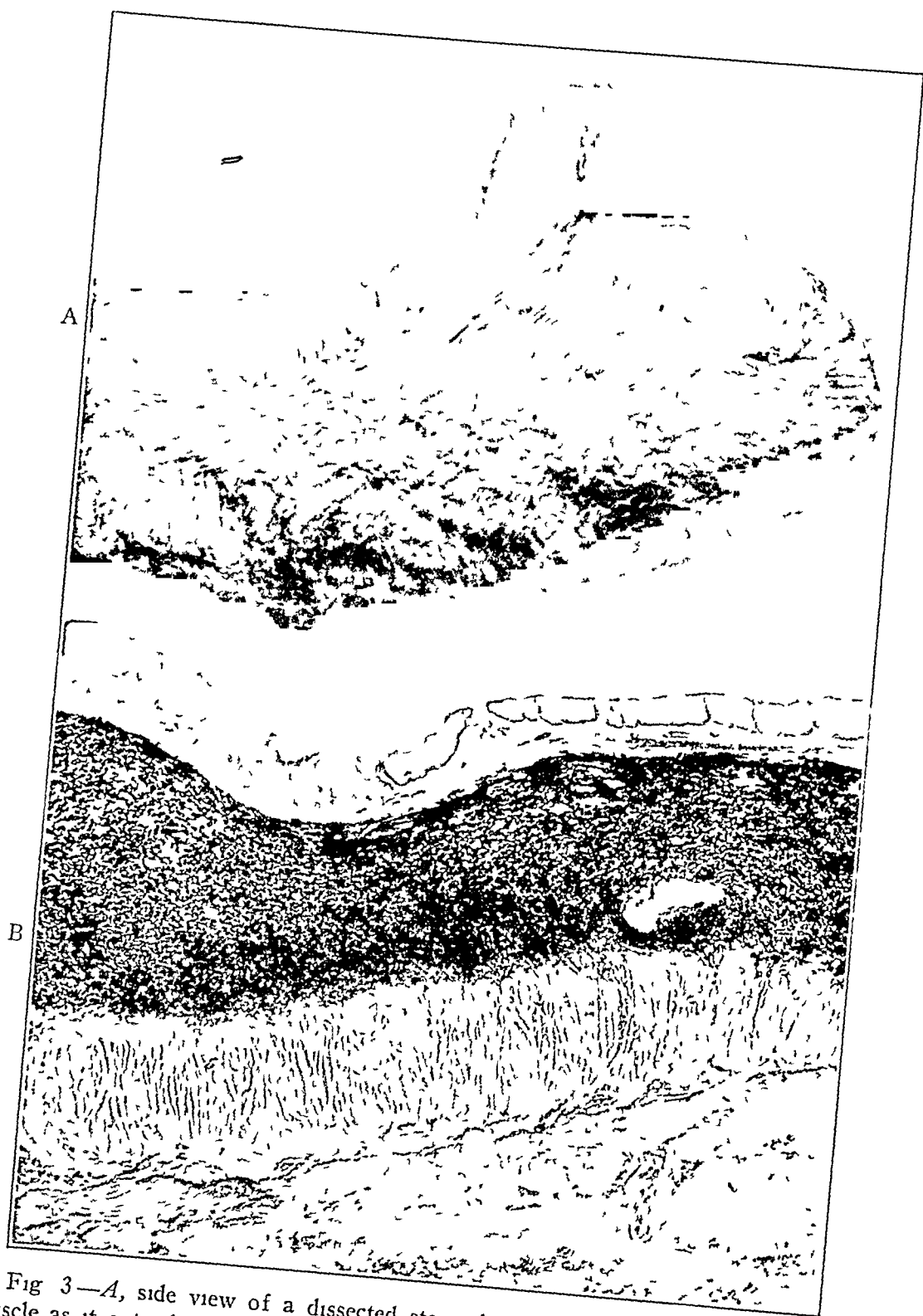


Fig 3—A, side view of a dissected stomach, showing an arm of the oblique muscle as it extends along one side of the lesser curvature and then loops around the terminal portion of the esophagus to join its fellow of the opposite side B, cross-section showing the injection mixture passing underneath the cardia in the submucosa ($\times 12$)

the elastic tissue of the esophagus is "most abundant in the submucosa, although a certain amount is scattered between the bundles of the two main muscles. The elastic tissue is greatest in amount at the lower end of the esophagus." This is true "even in the disorganized esophagus of cardiospasm" and also in the dog. "The terminal portion of the resting esophagus is closed. The deep vertical pleats and the abundant elastic tissue which is present at this point are the main factors in bringing this about." This statement that the elastic tissue functions in the closure of the cardia was made also by Stohr²⁵. He noted an increase in the amount of elastic tissue, however, in the muscular instead of the submucous layer at the cardia.

The issue here raised is of considerable importance. If, as the reports of these authors imply, the closure of the lower end of the esophagus and the cardiac orifice is a passive process caused by elastic tissue and if the opening of the cardiac orifice is the active process, the basic physiologic notions in terms of which writers have tried to explain cardiospasm will need to be radically revised.

In order to throw light on this problem, both longitudinal and transverse sections were taken from the middle portion of the esophagus, cardia, lesser curvature of the stomach and jejunum of five patients examined at necropsy. These specimens were stained with either the Weigert stain for elastic tissue or the Grubler stain for elastin and were examined microscopically.

The observations may be summarized as follows. At the cardia the elastic tissue is essentially the same in amount and arrangement as it is at the middle portion of the esophagus, with one exception, which will be noted presently. The mucosa superficial to the muscularis contains a few fine elastic fibers, which in the adult tend to form sheaths around the cardiac glands. Numerous coarser fibers, longitudinal in direction, are present between the strands of the muscularis mucosae. In the submucosa the elastic fibers, also longitudinal in direction, are more numerous than they are in the mucosa. The bulk of the elastic tissue, however, occurs in sheaths of the muscularis propria. There is an inner sheath between the circular muscle and the submucosa, an intermuscular sheath which splits to surround the ganglions of the myenteric plexus and a ragged and irregular adventitial sheath. The general direction of these sheaths is longitudinal, although numerous circular fibers are noted in connection with the inner circular muscle, and numerous radial strands connect the three layers. The adventitia of the cardia differs from that of the middle portions of the esophagus in that many more

²⁵ Stohr, Philipp. *Lehrbuch der Histologie und der mikroskopischen Anatomie des Menschen mit Einschluss der mikroskopischen Technik*, Jena, Gustav Fischer, 1919.

coarse longitudinal fibers are present in the former. The amount of elastic tissue gradually diminishes as sections from the esophagus to the jejunum are examined.

I have been unable to confirm the assertion of Mosher and McGregor that the submucosa of the cardia contains an exceptionally large amount of elastic tissue which functions in the closure of the cardia. Only in the adventitia of the cardia did I observe more elastic tissue than is present in similar sections from the middle portion of the esophagus. The adventitial fibers are longitudinal in direction, hence, they presumably do not have a constrictor action on the cardia.

LYMPHATIC DRAINAGE

My study of the lymphatic drainage at the cardia will be presented in abstract only. The continuity of the submucous space at the cardia was investigated by the method of Horton. In fifteen human specimens a dye and gelatin mixture was injected into the submucosa of the esophagus or of the stomach in the region of the cardia. In contrast to what Horton²⁶ observed at the pylorus, no submucous block was seen at this orifice of the stomach. The injection mixture passed freely in the submucosa, both from the stomach into the esophagus and from the esophagus into the stomach (fig. 3 B).

The lymphatic drainage of the cardia of the living cat was studied by injecting blebs of india ink into the submucosa of the terminal portion of the esophagus and by examining the viscera after intervals of from a half hour to two hours. In all cases drainage was found to occur through the adventitial lymph vessels to one or two lymph nodes at the bifurcation of the trachea and to one or two lymph nodes along the lesser curvature of the stomach. No trace of ink was seen in any other lymph node.

ARTERIAL ANASTOMOSIS

On account of the clinical importance of the esophageal varices which form in cases of portal obstruction, the venous anastomoses across the cardia have long received attention. Recently, Kegaries¹ made a careful anatomic investigation of this subject, and his work called attention to the variability in the amount of venous anastomosis across the cardia and to the richness of the submucous plexus of the esophagus. His

26 Horton, B. T. Pyloric Musculature with Special Reference to the Pyloric Block, *Am J Anat* **41** 197-225, 1928, A Study of the Pyloric Block with Special Reference to Musculature, Myenteric Plexus and Lymphatics, Thesis, University of Minnesota Medical School, 1930, Tr. A. Resid. & ex-Resid. Physicians, *Mayo Clin* **10** 152, 1930, Pyloric Block with Special Reference to the Musculature, Myenteric Plexus and Lymphatic Vessels, *Arch Surg* **22** 438-462 (March) 1931, footnote 20.

injections showed a band of parallel nonanastomosing veins which connect the submucous venous network of the stomach with that of the esophagus

Compared with the venous anastomoses, the arterial connections across the cardia have received little attention. Demel,²⁷ it is true, made a careful investigation of the arterial supply of the esophagus in 1924. Two features of his work, however, made me wish to obtain further enlightenment. First, his method of pumping injection mixture into the aorta and, hence, of injecting the mixture simultaneously into all the arteries which supply the esophagus is not one that outlines sharply the region supplied by any individual artery or that facilitates a comparison of the varying regions supplied in different specimens. Second, he said that the "fourth part of the esophagus reaches from the diaphragm to the cardia and is from 3 to 6 cm long." In my specimens, however, the length of the esophagus below the diaphragm was generally about 2 cm, which is the figure usually given in the textbooks. The larger figure given by Demel²⁷ suggested that the "abdominal portion of the esophagus," as defined by its blood supply, may extend considerably farther than the actual subdiaphragmatic segment of the esophagus—a consideration of some importance if true.

My problem was to determine the extent of the arterial connections across the cardia which come from the gastric vessels.

The method employed was that of injecting a radiopaque medium into the left gastric artery. Roentgenograms were made of the arterial tree thus outlined (fig. 4), and dissections were made to determine precisely the position and connections of each vessel revealed in the roentgenograms. Ten human specimens were employed. Great care was taken to eliminate such disturbing factors as the plugging of arteries by blood clots or the presence of pressure or kinking in the region of the cardia.

The most striking single fact demonstrated in the ten specimens was the extreme variability of the arterial connections from the stomach into the esophagus. In some cases the mixture was injected into the esophageal vessels for as far as 10 cm above the diaphragm. In such cases it is important to note that the esophagus is as richly supplied with vessels as is a similar portion of adjoining stomach. In other cases the mixture stopped abruptly at the cardia, even when the uniform injection of mixture into the stomach indicated that the arterial system was free from blood clots. Most frequently, however, a single branch or a few branches pass from the gastric arteries to supply limited portions of the

27 Demel Rudolf. Die Gefässversorgung der Speiseröhre. Ein Beitrag zur Oesophaguschirurgie, Arch f Klin Chir **128** 453-504, 1924.

esophagus—not predominantly the right posterior aspect of the esophagus, as Demel²⁷ has alleged, but portions which vary greatly in size, shape and position

All the branches of gastric arteries which supply any large portion of the esophagus ascend in the adventitia. The most frequent arrangement is for one large vessel or group of vessels to ascend on the posterior surface of the esophagus and for another vessel or group of vessels to ascend on the anterior surface. These arteries anastomose freely with each other and usually also with the lowest esophageal arteries, which arise from the aorta and which are most frequently seen about 12 cm above the cardia. I did not make roentgenograms of the diaphragm, but as far as gross dissection could reveal, connection with the diaphragmatic arteries appeared small and infrequent.



Fig. 4—Roentgenograms of the arteries of two stomachs, showing the striking difference in the extent of the anastomoses in the lower portion of the esophagus.

The adventitial arteries give off three types of branches. The first type consists of sparse branches which supply the adventitia itself. The second type consists of the numerous but tiny branches which supply the esophageal muscles. These branches generally penetrate to the intermuscular septum and then break up into tiny twigs. The arterial branches which penetrate to the intermuscular septum doubtless communicate with each other and with the arterioles in the intermuscular septum of the stomach, but the anastomoses are so small that I could not demonstrate them in my dissections. The third type of branches of the adventitial arteries consists of relatively large trunks which penetrate through the muscular layer at intervals of about 2 cm and enter the

submucosa In the submucosa they break up into a fine network of anastomoses which resemble the venules of a leaf At the cardia this network communicates freely with the submucous plexus of the stomach There is no band of straight nonanastomosing vessels connecting the two networks across the cardia, such as Kegaries has observed in the venous anastomosis On the contrary, the same architecture is observed in the network which crosses the cardia as in the adjoining esophagus and stomach It is important to note, however, that the anastomoses in the submucosa are fine and hairlike and incapable of carrying the injection mixture more than a couple of centimeters up the esophagus if the adventitial arteries are occluded

NERVES (MYENTERIC PLEXUS)

If there is no sphincter or muscular discontinuity at the cardia to explain the functional changes which occur at this point, one must look for their explanation in the nervous mechanisms of the cardia Even if the controversial phenomenon of clinical cardiospasm is left out of consideration, it must be recognized that the cardia is the site of important changes in function that distinguish this region not only from the adjoining stomach but also from the portions of the esophagus which lie above it First, there is the action as a physiologic sphincter Second, there is the phenomenon of experimental spasm of the circular muscle at the cardia (not necessarily identical with clinical cardiospasm), which may be produced by cutting the vagi or reflexly by stimulating various abdominal viscera, as Carlson, Boyd, Percy and Luckhardt,²⁸ Scrimger,²⁹ and others have demonstrated Third, although Alvarez³⁰ stated the opinion that the peristaltic waves of swallowing may pass across the cardia and continue as peristaltic waves of the stomach, it is obvious that there is a discontinuity at the cardia between the rapid and voluntarily initiated waves of swallowing and the slower and rhythmic movements of the stomach

The myenteric plexus (Auerbach's plexus) is a network of nerve fibers, mostly unmyelinated, which lies between the inner circular and outer longitudinal muscular layers of the enteric canal and which

28 Carlson, A. J., and Luckhardt, A. B. Studies on the Visceral Sensory Nervous System. X. The Vagus Control of the Esophagus, *Am J Physiol* **57** 299-335 (Sept.) 1921. Carlson, A. J., Boyd, T. E., and Percy, J. F. Studies on the Visceral Sensory Nervous System. XIII. The Innervation of the Cardia and the Lower End of the Esophagus in Mammals, *ibid* **61** 14-41 (June) 1922, XIV. The Reflex Control of the Cardia and the Lower Esophagus in Mammals *Arch Int Med* **30** 409-433 (Oct.) 1922.

29 Scrimger, F. A. C. Idiopathic Dilatation of the Oesophagus, *Ann Surg* **94** 801-817 (Nov.) 1931.

30 Alvarez, W. C. Personal communication to the author.

extends from the upper portion of the esophagus to the terminal portion of the rectum. This plexus is uniformly distributed on all sides of the alimentary canal. At the nodal points of the network, ganglions occur. Krishnan³¹ and others have demonstrated that the myenteric plexus functions to control or at least to coordinate the movements of the gastro-intestinal tract.

The myenteric plexus presents the same appearance at the cardia as it does throughout the lower two thirds of the esophagus. It is cut about once a millimeter in microscopic sections passing through the intermuscular septum. It is a less conspicuous structure at the cardia than it is in the small intestine, because it is surrounded by connective tissue instead of lying naked between the muscular layers. The ganglions are made up of nerve fibers, ganglion cells and sustentacular cells. I have tried a wide variety of special stains but have not found any that can approach the ordinary Van Gieson stain in rendering the ganglion cells easily visible so that the cells can be counted.

Ganglion cells appear in variable numbers in the ganglions at the cardia, occasionally, a favorable section may show as many as ten cells in one ganglion. They are roughly oval, with the long axis parallel to the long axis of the esophagus. When stained with the Van Gieson stain they present a striking appearance. They are far larger than any other cells which may be seen in this region. The cytoplasm, which stains a dark brownish gray, is equally distinctive. The large, clear nuclei, each with a large nucleolus, are also specific. Finally, each ganglion cell is surrounded by a capsule of sustentacular cells. The latter, which have numerous other names, are apparently insulating cells which correspond to the cells of the sheath of Schwann and the oligodendroglia cells in the peripheral nerves and the central nervous system, respectively.

Dogiel³² described two types of ganglion cells in the myenteric plexus, the distinction resting chiefly on the differences in the dendrites, as revealed by the vital methylene blue stain. He said that one type represents ganglion cells of the sympathetic system and that the other type represents ganglion cells of the vagus nerve. The evidence on the subject has been critically evaluated by Gaskell³³ and more recently by Kuntz³⁴. The weight of authority favors the view that all the ganglion

31 Krishnan, B. T. Studies on the Function of the Intestinal Musculature. Are Intestinal Movements Neurogenic or Myogenic? *Quart. J. Exper. Physiol.* **22** 361-368 (June) 1933.

32 Dogiel, A. S., quoted by Gaskell³³.

33 Gaskell, W. H. *The Involuntary Nervous System*, London, Longmans, Green & Co., 1916.

34 Kuntz, Albert. *The Autonomic Nervous System*, Philadelphia, Lea & Febiger, 1929.

cells of the myenteric plexus in the esophagus, cardia and stomach represent terminal ganglion cells of the vagus nerve. Sympathetic fibers are not present in the esophagus, except in the last few centimeters above the cardia. Here, they mingle with the fibers of the myenteric plexus but pass through the ganglions without synapse. There is certain physiologic evidence which indicates the presence of independent local reflex arcs in the wall of the intestine, which are mediated by the myenteric plexus. The anatomic evidence is all against such a view, however³⁵

The question of the continuity of this nervous network from the esophagus into the stomach has a good deal of physiologic significance, yet I have found that only two authors have investigated the subject. One was Irwin,³⁶ who used the vital methylene blue technic, who reported that in the guinea-pig he had traced some nerve fibers from the esophagus to ganglions in the stomach. The second author was Sir Arthur Keith. After discovering in the heart the node which now bears his name—the sino-auricular node—Keith³⁷ began to find similar nodes almost everywhere. He has described several of them situated at strategic points in the gastro-intestinal tract. Among other places he claimed to have found a “definite development of neuromuscular junctural tissue” at the cardia. No other anatomist has confirmed Keith’s work. His illustrations look to me like those of an ordinary myenteric plexus. None of my sections of the cardia showed any structure that could be interpreted as neuromuscular junctural tissue. One can hardly escape feeling that the junctural node at the cardia belongs in the same category as the unicorn and the basilisk.

As will be demonstrated in a later section of this paper, lesions of the myenteric plexus are an important subject in relation to the pathogenesis of cardiospasm. The lesions are ordinarily described in terms of numerical loss of ganglion cells as seen in microscopic sections of the myenteric plexus. It is accordingly important to establish a norm for the number of ganglion cells appearing in a standard microscopic section. But before this is done, it is necessary to point out that if the

35 Alvarez, W. C. *The Mechanics of the Digestive Tract. An Introduction to Gastroenterology*, New York: Paul B. Hoeber, Inc., 1928.

36 Irwin, D. A. *The Anatomy of Auerbach’s Plexus*, *Am J Anat* **49** 141-166 (Sept.) 1931.

37 Keith, Arthur. *An Account of Six Specimens of the Great Bowel Removed by Operation, with Some Observations on the Motor Mechanism of the Colon*, *Brit J Surg* **2** 577-599, 1915, *A New Theory of Enterostasis*, *Lancet* **2** 371-375 (Aug. 21) 1915, *Discussion on the Interpretation of Certain X-Ray Signs of Intestinal Stasis*, *Proc Roy Soc Med (Electrotherap Sect)* **9** 1-11, 1916, *The Great Bowel, from an Anatomist’s Point of View*, in Lane, W. A. *The Operative Treatment of Chronic Intestinal Stasis*, ed. 4, London, Hodder & Stoughton, 1918, pp. 202-217.

ganglion cells of the myenteric plexus, like those elsewhere in the body, do not increase in number after birth, then the esophagus in the adult can contain no more ganglion cells than the esophagus of the new-born infant. This same number of ganglion cells, moreover, is distributed over a longer and wider esophagus in the adult, and fewer cells can be expected to appear in a microscopic section of given dimensions. Furthermore, in the dilated esophagus in a case of cardiospasm the mean distance between ganglion cells must be still further increased, and even without any destruction of ganglion cells one must expect the number of cells in any microscopic section to be greatly reduced.

In order to determine the normal number of ganglion cells to be expected in a microscopic section at the cardia, counts were made on two hundred segments of the myenteric plexus appearing in sections of the cardias of fifty-eight adults. In all cases the cardia appeared grossly and microscopically normal. The fifty-eight persons included forty-one men and seventeen women. The range in age for the men was from 22 to 87 years, with an average age of 56.85 years. The range in age for the women was from 18 to 78 years, with an average age of 48.17 years. In these fifty-eight cases eighty-nine blocks of tissue were taken. One hundred and thirty-nine sections were made. The sections were 8 microns thick and were cut in a longitudinal direction, perpendicular to the surface. The sections were mostly stained by the Van Gieson method. According to the length of the section, one or two segments, which were 1 cm. in length, were measured along the myenteric plexus and marked on the cover glass, and the number of ganglion cells present in such segments was counted with the aid of a microscope. It will be understood that not every ganglion cell was cut squarely through the center in such a way as to reveal all its characteristic features. Only such structures were counted as ganglion cells, however, as were sufficiently intact to be identified unquestionably as such. Twelve hundred and fifty ganglion cells were counted in 200 segments, which were 1 cm. long. The results are presented in table 1. The curve that shows the frequency of these cells has an interesting skew shape (fig. 5). The wide range of the various counts and the large probable error emphasize the necessity for making multiple counts of cells before concluding that the number of ganglion cells is abnormal in cardiospasm or in any other condition.

The range of values found when multiple counts were made with sections from a single cardia confirms these conclusions. A comparison of the number of ganglion cells in specimens obtained from a small group of young adults with the number of ganglion cells in specimens obtained from a similar group of aged adults suggested that there may be some loss of ganglion cells with advancing years.

CARDIOSPASM

Some of the anatomic features of the normal cardia have already been described It is now my intention to apply these norms to the study of specimens from patients with cardiospasm It is my purpose

TABLE 1—Data on the Number of Ganglion Cells in Centimeter Segments of the Myenteric Plexus at the Cardia *

Number of Ganglion Cells	Number of Times Observed	Number of Ganglion Cells	Number of Times Observed
0	24	16	5
1	19	17	4
2	18	18	1
3	16	19	1
4	16	20	1
5	18	21	1
6	11	22	1
7	7	23	1
8	12	24	0
9	10	25	0
10	8	26	0
11	6	27	0
12	9	28	0
13	4	29	1
14	4	30	0
15	2		

* Segments counted, 200, ganglion cells counted, 1,250, mean number of ganglion cells per segment, 6.25, mode, 0, standard deviation, ± 5.48 , probable error, ± 3.69

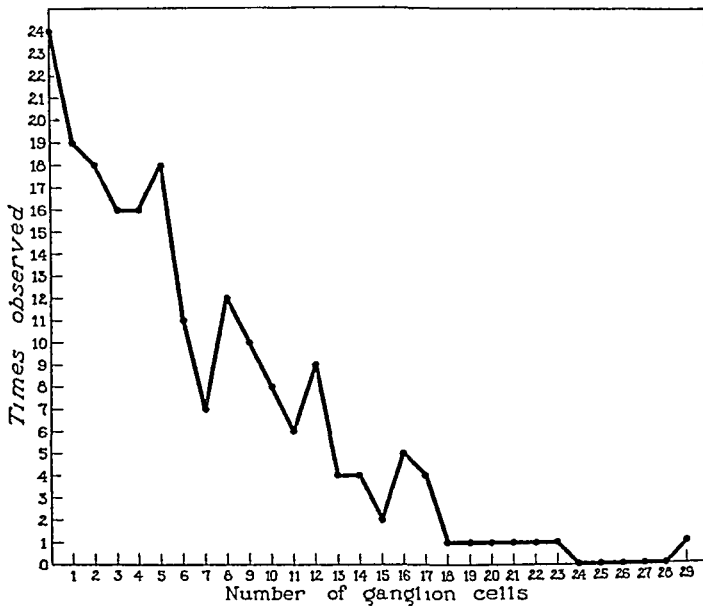


Fig 5—Graph showing the frequency of ganglion cells in segments of the myenteric plexus 1 cm in length

to lay aside clinical preconceptions as to the nature of cardiospasm and to study the available material simply as examples of a chronically dilated esophagus without evident organic obstruction Even the report of clinical histories will be reduced to the minimum of facts such as

the duration of symptoms, operative treatment and coincidence with the onset of some acute infectious disease, which are directly pertinent to the interpretation of the anatomic findings

Hurst recently has pushed the history of cardiospasm back a century and a half by calling attention to a remarkable case recounted in 1672 by Thomas Willis³⁸ in his "Pharmaceutice rationalis." Willis not only divined the true nature of the condition but even treated it successfully with dilation. The honor of describing the first case of idiopathic dilatation of the esophagus, however, is usually attributed to Purton³⁹ in 1821. Hannay⁴⁰ (1833) is generally credited with the second case, although Herbert Mayo⁴¹ performed a necropsy in one case in 1829. Zenker⁴² and von Ziemssen were the first to recognize the condition as a clinical syndrome (in 1876). They collected reports of seventeen cases from the literature and applied to the disease the name simple ectasia of the esophagus. Following this numerous cases were reported, chiefly from Germany, but it remained for Plummer⁴³ and his associates to appreciate the great clinical importance of cardiospasm and to discover highly accurate methods of diagnosis and a satisfactory procedure of treatment. The literature on cardiospasm was reviewed in German in 1921 by Thieding⁹ and in English in 1933 by Sturtevant⁴⁴.

In 1882 von Mikulicz⁴⁵ coined the catchy but question-begging term cardiospasm. This name is as unfortunate as would have been the designation anospasm for Hirschsprung's disease, because the view that chronic dilatation of the esophagus results from a spasm of the circular muscle at the cardia is by no means universally accepted. For example, Bassler⁴⁶ has said that what is called cardiospasm is in reality a constriction of the lower end of the esophagus by the crura of the

38 Willis, T, quoted by Hurst^{71b}

39 Purton, J, quoted by Sturtevant⁴⁴

40 Hannay, A. J. An Extraordinary Dilatation (with Hypertrophy) of All the Thoracic Portion of the Esophagus, Causing Dysphagia, Edinburgh M. & S. J. **40** 65-72, 1833

41 Mayo, Herbert. Outlines of Human Pathology, Philadelphia, A. Walde, 1839

42 Zenker, F, in von Ziemssen, H. Handbuch der speciellen Pathologie und Therapie, Leipzig, F. C. W. Vogel, 1876

43 Plummer, H. S. Cardiospasm with Report of Cases, J. Minnesota M. A. **26** 419-424, 1906, Cardiospasm with Report of Forty Cases, J. A. M. A. **51** 549-554 (Aug. 15) 1908

44 Sturtevant, Mills. Cardiospasm, with a Review of the Literature, Arch. Int. Med. **51** 714-736 (May) 1933

45 von Mikulicz, J, quoted by Sturtevant⁴⁴

46 Bassler, Anthony. Cardiospasm. What It Is, What It Seems to Be, New York State J. Med. **14** 9-11, 1914

diaphragm Chevalier Jackson ⁴⁷ and others have further developed this theory and have suggested that this clinical syndrome be termed phienospasm Zenker,⁴² Rosenheim,⁴⁸ Bier ⁴⁹ and Sternberg,⁵⁰ however, have asserted that in cardiospasm the cardia is no more firmly closed than it normally is but that the failure is the result of paralysis of the esophagus, so that the function of forcing food through the cardiac orifice is not exercised Huist stated that the "law of the intestine" applies at least to the cardiac end of the esophagus and gave as his opinion that so-called cardiospasm is really a failure of the normal reflex relaxation of the cardia in swallowing Accordingly, he applied to the condition the term achalasia of the cardia Mosher has entertained at various times the theories that the obstruction to swallowing is caused by pressure on the esophagus by the tips of the lungs, by compression by the "liver tunnel," ⁵¹ by kinking and torsion of a redundant esophagus ⁵² and by fibrosis of the periesophageal connective tissue ⁵³

The study of cardiospasm is handicapped by something which impedes the study of few diseases, namely, the extraordinary effectiveness of the methods available for treatment Despite the frequency of the condition, so few persons die of cardiospasm at the various medical centers that I have found no reports of necropsy which comprise more than thirteen cases

Some evidence has accumulated, however, to support the view that cardiospasm is associated with definite lesions of nerves Cameron ⁵⁴ has reported lesions of Auerbach's plexus in seven cases of cardiospasm in children Heyrovsky ⁵⁵ noted vagus neuritis at necropsy in cases of cardiospasm, and Loeper and Forestier ⁵⁶ have reported recurrent spasm

47 Jackson, Chevalier The Diaphragmatic Pinchcock in So-Called "Cardiospasm," *Laryngoscope* **32** 139-142 (Feb) 1922

48 Rosenheim, T, quoted by Sturtevant ⁴⁴

49 Bier, August Die Erklärung der Ischuria paradoxa und des Kardiospasmus, *Zentralbl f Chir* **58** 901-902 (April 11) 1931

50 Sternberg, W, quoted by Sturtevant ⁴⁴

51 Mosher, H P Liver Tunnel and Cardio-Spasm, *Laryngoscope* **32** 348-362 (May) 1922

52 Mosher, H P Cardiospasm, *Pennsylvania M J* **26** 240-249 (Jan) 1923

53 Mosher, H P Fibrosis of the Terminal Portion of the Esophagus Cardiospasm, *Proc Internat Assemb Inter-State Post-Grad M A, North America* **6** 95-104, 1931

54 Cameron, J Oesophagectasia in a Child, *Arch Dis Childhood* **2** 358-360 (Dec) 1927

55 Hevrovsky, Hans Casuistik und Therapie der idiopathischen Dilatation der Speiseröhre Oesophagogaströanastomose, *Arch f klin Chir* **100** 703-715 (Jan 30) 1913

56 Loeper, M, and Forestier, J Les lésions nerveuses du pneumogastrique et le cardiospasmie recurrent dans le cancer de l'estomac, *Arch d mal de l'app digestif* **11** 307-312, 1921

at the cardia in carcinoma of the stomach that was complicated by ascending invasion of the vagus by tumor cells Kraus and Pollitzer⁵⁷ also have reported lesions of the vagus nerve in cardiospasm Finally, Hurst and Rake,⁵⁸ Stokes,⁵⁹ Rake,⁶⁰ Cameron,⁵⁴ Beattie⁶¹ and Mosher and McGregor have reported a loss of ganglion cells in the myenteric plexus in cases of cardiospasm Whether this is primary or secondary is a controversial point Mosher, who already has an excess of theories with which to explain cardiospasm, stated that he was inclined to think that the loss of ganglion cells is secondary to the pressure which the distended esophagus suffers He quoted Cannon¹² to show that the ganglion cells of the myenteric plexus are highly susceptible to pressure anemia Hurst, on the other hand, concluded that "achalasia of the cardia," as he termed the condition, is primarily an organic disease of Auerbach's plexus

Cardiospasm is frequently associated with diverticulum of the esophagus Sturtevant listed Vinson,⁶² Fitzgibbon,⁶³ Bull,⁶⁴ Dufour,⁶⁵ Van den Wildenberg⁶⁶ and Freud⁶⁷ as reporting cases of this concurrence The association of cardiospasm with asthma has been noted by Scollery,⁶⁸ von Bergmann⁶⁹ and Lindvall⁷⁰ The condition most commonly found in association with cardiospasm, however, is peptic ulcer Heyrovsky⁵⁵ and many others have commented on this fact Syphilis is not often found in conjunction with cardiospasm, and in none of the following cases was syphilis present

REPORT OF CASES

The specimens in the following thirteen cases were examined grossly, and from twenty-five to one hundred sections of each specimen afterward were studied microscopically Each case will be described briefly, and then the findings for the whole group will be summarized

57 Kraus and Pollitzer, quoted by Mosher and McGregor^{24a}

58 Hurst, A F, and Rake, G W Achalasia of the Cardia (So-Called Cardiospasm), *Quart J Med* **23**:491-508 (July) 1930

59 Stokes, A, quoted by Hurst^{71b}

60 Rake, G, quoted by Hurst^{71b}

61 Beattie, W J H M, quoted by Hurst^{71b}

62 Vinson, P P Cardiospasm Associated with Esophageal Diverticula, *New York M J* **117** 540 (May 2) 1923

63 Fitzgibbon, J H, quoted by Sturtevant⁴⁴

64 Bull, P N, quoted by Sturtevant⁴⁴

65 Dufour, H, quoted by Sturtevant⁴⁴

66 Van den Wildenberg, L, quoted by Sturtevant⁴⁴

67 Freud, J, quoted by Sturtevant⁴⁴

68 Scollery, quoted by Sturtevant⁴⁴

69 von Bergmann, quoted by Sturtevant⁴⁴

70 Lindvall, H quoted by Sturtevant⁴⁴

CASE 1—A man aged 53 had suffered from salivation and progressive dysphagia for five years before he came to the Mayo Clinic. A roentgenogram revealed not only dilatation of the esophagus but a perforating ulcer on the lesser curvature of the stomach. The ulcer was excised, and the cardia was manually dilated in the course of the operation. The patient made an uneventful convalescence. Eleven days after the operation he was dismissed from the hospital and was waiting for a bus, when he suddenly dropped dead on the sidewalk.

The general observations at necropsy included old healed aortic and mitral endocarditis with stenosis, hypertrophy and dilatation of the heart, arteriosclerotic changes in the kidneys, fatty changes in the heart, liver and kidneys, multiple diverticula of the rectum, moderate general arteriosclerosis, and thrombosis of the prostatic plexus. The partial excision by knife of the gastric ulcer had healed without perforation or peritonitis. Death was attributed to cardiac failure.

Examination of the stomach and esophagus revealed contraction without organic narrowing of the lowest 4 cm. of the esophagus. There was a fusiform dilatation, which proceeded from below upward to a sac which had a maximal inner circumference of 8 cm. at a point 9 cm. above the juncture of the esophageal and the gastric mucosa. There was no evidence of ulceration, scarring or rupture of the esophagus, no diverticulum, twisting or kinking of the esophagus was present and there was no suggestion of a hypertrophied sphincter or of hypertrophy of the oblique muscle of the stomach.

Microscopic examination showed that in the undilated portion of the esophagus, at and just above the cardia (I shall call this portion the neck), the epithelium was relatively thickened, but otherwise it was normal. In the dilated portion of the esophagus (the sac) the epithelium was thinner and was eroded in some places but not ulcerated. The neck revealed a relative thickening of both layers of the muscularis propria and a slight increase in the amount of elastic tissue. In the sac the amounts of muscle and of elastic tissue were approximately normal, but the circular elastic fibers were more prominent than usual. There was no fibrosis among the muscle fibers. The ganglion cells of the myenteric plexus had almost disappeared (fig. 6). No cells were seen in sixteen segments of the cardia, which were 1 cm. in length, and in nine similar segments of the sac. The ganglions of the myenteric plexus showed a great increase in the number of nuclei in the supporting (sustentacular) cells. These cells frequently formed little whorls inside what appeared to be the capsules of former ganglion cells. Such whorls presented a superficial resemblance to renal glomeruli, for want of a better label they will be termed glomeruloids. As was true in many of these cases, the largest part of the vagus nerve had been removed by the laboratory technician in the process of making a neat looking specimen for display. Numerous fragments of the vagus plexus were discovered, however, and studied with special stains for nerves, but all were normal.

CASE 2—A woman aged 29 came to the clinic because of dysphagia, which had been present for two years. In the previous six months she had undergone ten dilations of the esophagus for cardiospasm. Seven days before she came to the clinic she had submitted to dilation elsewhere, which had been followed by fever and soreness and swelling of the neck. At the time the patient came to the clinic advanced cellulitis of the neck, stridor, dyspnea and cyanosis were present. She died the following day.

Necropsy revealed rupture at the upper end of the esophagus, with multiple and extensive communicating retropharyngeal and pretracheal abscesses. Thy-

roidectomy, which had been performed ten years previously, was found to have left extensive scars around the trachea and carotid sheaths. The examination did not reveal anything else of consequence.

Examination of the specimen did not reveal organic constriction of the neck of the cardiospasm. It extended for about 1 cm above the mucosal junction. There was a fusiform dilatation that extended to a sac, which was 28 cm long but only 5.4 cm in its greatest circumference. The walls of the sac were thick, and the mucosa was puckered in the lower portion. On the left side of the esophagus, 12 cm below the cricoid cartilage, was a perforation which measured 1 by 4 mm. There was no evidence of ulceration, kinking, scarring or diverticulum of the esophagus.

Microscopic study disclosed that the epithelium was normal throughout, except for a few erosions. There was no ulceration. Sections through the edges of the perforation demonstrated that the rupture was through the sound esophagus and



Fig 6—A ganglion in the myenteric plexus in case 1 ($\times 235$). Ganglion cells are absent, and the proliferating cells have taken on an appearance which some observers have confused with that of lymphocytes. At the right is an imperfect example of one of the whorls of cells which I have labeled a glomeruloid.

that it had not been preceded by scarring or ulceration. The edges of the perforation were the site of a violent pseudomembranous inflammation. Diffuse inflammation, with many polymorphonuclear leukocytes, had spread in the mucosa as far as the cardia. It had not spread so far in the intermuscular septum, but it involved the myenteric plexus. Infection had extended a still smaller distance in the submucosa and in the adventitia. Both muscular layers were greatly thickened throughout the entire length of the sac, and the circular muscle measured 0.5 cm in thickness. The muscle did not reveal any fibrosis or special band at the cardia. The density of the elastic tissue was increased in the lower two thirds of the esophagus, but it became thin in the upper third. Ganglion cells had mostly disappeared, none were seen in three segments of the cardia, and only two were

present in seventeen segments of the sac. In the lower part of the esophagus the ganglions showed proliferation of supporting cells and the formation of glomeruloids, in the upper part the ganglions were involved in acute inflammation. The vagus nerve appeared normal on section.

CASE 3—A woman aged 39 had suffered from increasing difficulty in swallowing for seventeen years, with regurgitation of undigested food after eating. Dilation of the esophagus was followed at once by colic and evidence of pleuritis on the left side. The following day 1,200 cc of fluid was aspirated from the left pleural cavity. Afterward posterior mediastinotomy was performed for rupture of the esophagus. Two days later subcutaneous emphysema of the neck developed. The patient died on the seventh day after the operation.

Necropsy revealed rupture of the esophagus, widespread mediastinitis, empyema on the left side, collapse of the left lung, recent resection of the ninth and tenth ribs on the left side posteriorly and terminal pleuritis at the base of the right lung. Old healed tuberculous pleuritis and lymphadenitis, cysts of the ovaries, polyps of the uterus, papillomas of the bladder, Meckel's diverticulum and moderate arteriosclerosis also were noted. The esophagus was dilated. The laceration, which was 1.5 cm long, was longitudinal in direction and extended upward from a point 1.5 cm above the mucosal junction. Considerable thickening of the neighboring diaphragm was noted.

No gross organs could be removed, hence my study was limited to small fragments of tissue which showed the rupture and thickening of the mucosa of the terminal portion of the esophagus. Microscopic study showed the epithelium to be thickened, with beginning cornification, which was of the mucous membrane type. No ulceration was present. Sections from the borders of the tear in the esophagus showed it to be the site of acute pseudomembranous inflammation. There was no evidence of old ulceration or thinning of the muscular layers at this point. The infection had extended for some distance in the submucosa. The strands of the circular muscle, just above the cardia, appeared to be pulled apart and showed regions of necrosis without infection. As will be demonstrated later, this appearance of the circular muscle is not infrequently found in cases of cardiospasm after dilation. There was no fibrosis in the muscular layers, and the elastic tissue appeared normal. In twenty-three segments of the myenteric plexus, which were 1 cm in length and from the cardia, a total of thirteen ganglion cells were seen, most of them in various stages of degeneration. There was an increase in the number of nuclei in the supporting cells in the ganglions, and numerous glomeruloids were seen. Sections from the vagus nerve were normal.

CASE 4—A youth aged 17 years always had been regarded as enjoying perfect health. When his mother was questioned in the light of the postmortem observations, however, she related that ever since childhood he had been accustomed to regurgitate food after eating. The food had come up easily and without retching. He had learned not to eat too much at a time and to keep a basin beside him while he ate. On Sept. 23, 1924, the patient had engaged in football practice until 6 p. m. He had remained with his companions until 7 p. m. and then had come home. His parents had found him dead on the floor at 9 p. m. There had been spontaneous evacuation of the bowels and bladder. A medicolegal necropsy was performed by Dr. H. E. Robertson. The esophagus was observed to be dilated and its wall was somewhat hypertrophied. There was generalized lymphadenopathy, but none of the lymph nodes was more than 1 cm in diameter. Arteriosclerosis was slight. The remainder of the examination, including the examination of the brain and of the organs of the neck, and toxicologic examination of the gastric contents, did not reveal anything to explain the cause of death.

The esophagus was dilated almost the entire distance from the cardia to the cricoid cartilage. Its size was normal for about 15 cm above the juncture with the gastric mucosa, then there was gradual dilatation to a maximal circumference of 8 cm at a point 9 cm above the cardia. The thickness of both the mucosal and the muscular layer was increased in the lower part of the esophagus but normal above. No diverticulum, ulceration or evidence of kinking or twisting of the terminal portion of the esophagus was noted. No special sphincteric muscular band or increased prominence of the oblique muscle of the stomach was observed.

Microscopic study revealed a general thickening of the epithelium. No ulceration or inflammation was present. Both muscular layers were thickened in the neck and in the lower part of the sac, the circular muscle had attained a thickness of 4 mm. In the upper part of the sac the thickness of the muscle was normal. Some vacuolar degeneration was present in the thickened circular muscle, but there was no fibrosis. The elastic tissue was slightly more prominent than normal. There was a general loss of ganglion cells in the myenteric plexus, eight segments of the cardia and lower and middle portions of the sac revealed a total of only three ganglion cells. At the upper end of the esophagus two segments revealed two and five ganglion cells, respectively. The degree of the proliferative changes in the ganglions was only moderate. No specimen of the vagus nerve could be obtained.

CASE 5—A woman aged 66 came to the clinic after she had suffered for eight years from intermittent attacks of dysphagia and salivation. During the previous eighteen months the symptoms had become much worse. Dilatation of the cardia was followed at once by substernal discomfort. The following day there was severe abdominal pain, and the next day auricular fibrillation, pleural effusions on both sides, dyspnea and paralysis of the left arm were present. The patient died on the third day after the operation.

Necropsy revealed that the esophagus had ruptured in the course of dilation and that there were consequent mediastinitis, bilateral empyema and purulent peritonitis of the lesser peritoneal sac. Mural thrombi were present in the left ventricle, and a diagnosis of multiple cerebral emboli was made on the basis of the clinical findings. Advanced emaciation, old healed tuberculous pleuritis and lymphadenitis, moderate arteriosclerosis, atrophy of the liver and arteriosclerotic changes in the kidneys also were noted.

The esophagus was dilated to a fusiform sac, which had a maximal circumference of 8 cm at a point 11 cm above the cardia. The circumference of the lower few centimeters of the esophagus was approximately normal. Beginning 0.5 cm above the mucosal junction on the left side of the esophagus, there was a longitudinal tear 2.5 cm in length. Several large lymph nodes were seen around the esophagus. No ulceration, diverticulum or evidence of kinking of the terminal portion of the esophagus was observed.

Microscopically the epithelium was observed to be thickened near the cardia, it was eroded but not ulcerated in the sac. The rupture passed through a region where the mucosa and muscular layer previously had been normal. The edges of the rupture were covered with acute pseudomembranous inflammation. Violent infection and inflammation, with necrosis, hemorrhage and masses of polymorphonuclear leukocytes, had spread in the submucosa, in the intermuscular septum and especially in the adventitia of the esophagus for a long distance as a result of the rupture. Both muscular layers were thickened in the neck and in the lower portions of the sac. There was no fibrosis of the muscular layer. The elastic tissue was normal throughout, except that the circular fibers were a little more prominent

than normally in the sac. Ganglion cells were numerous in the myenteric plexus of the stomach, near the cardia, but there were none in the terminal portion of the esophagus and in the sac of the cardiospasm. No ganglion cells were seen in twenty-five segments of the neck and of the lower and middle portions of the sac. At the extreme upper end of the esophagus, however, twenty-one ganglion cells were seen in five segments. There appeared to be little proliferation of the supporting cells, but the widespread infection in the intermuscular septum following the rupture made this difficult to judge. Sections of the vagus nerve were normal.

CASE 6—A girl aged 8 years had begun to have increasing esophageal obstruction after whooping cough three years before she was brought to the clinic. For a year and a half the obstruction had been extreme. When she arrived at the clinic she was too weak to allow any manipulation, and she died six days later.

Necropsy revealed advanced dilatation and hypertrophy of the esophagus, extreme emaciation and terminal bronchopneumonia, with edema of the glottis.

The circumference of the lowest 15 cm of the esophagus was about normal (25 cm). Above this there was gradual dilatation to a circumference of 75 cm at a point 7 cm above the cardia. The total length of the sac was 16 cm. On the left anterior surface of the sac there was a scar measuring about 2.5 by 0.3 cm, which was longitudinal in direction. It extended through all layers of the esophagus and involved a lymph node externally. Within a few centimeters of the scar were eight lenticular ulcers of the mucous membrane, each measuring about 0.5 by 0.2 cm. There was no diverticulum or kinking of the esophagus.

Microscopic examination showed a thickening of the epithelium, especially in localized islands. The ulcers which have been mentioned were subacute or chronic. They penetrated the muscularis mucosae and rested on the circular muscular layer. From the bases of each ulcer, strands of lymphocytes and endothelial cells extended between the muscular bundles to the intermuscular septum. Traces of the same infectious process were observed throughout the entire esophagus, in the submucosa, between the muscular bundles and in the adventitia, but especially in and around the ganglions of the myenteric plexus. Both muscular layers were increased in thickness. There was a slight increase in the amount of connective tissue in the septum of the circular muscular layer. Twenty-five segments of the cardia and sac did not reveal any ganglion cells, these segments were 1 cm long. Besides the chronic infection (which may apparently be traced to the myenteric plexus from the ulcers of the mucosa), the ganglions were enmeshed in much hyaline scar tissue. Sections from the vagus nerve appeared normal.

CASE 7—A man aged 58 had suffered from dysphagia for twenty years, and regurgitation of food and water had occurred for five years. Dilatation of the cardia was accompanied with slight pain and bleeding. An hour later he vomited blood and complained of severe pain in the abdomen and in the left side of the thorax. He failed rapidly and died on the second day after the operation.

Necropsy disclosed that a rupture of the esophagus had been followed by hemorrhage and pleurisy in the left pleural cavity. The left lung was totally collapsed and covered with grayish white exudate. Advanced emaciation, old healed tuberculous pleuritis and pneumonitis and a small adenoma of the thyroid gland also were present.

The esophagus was greatly thickened but moderately dilated, the greatest circumference being 56 cm at a point 108 cm above the cardia. The transition from the neck to the sac was gradual. Beginning 0.8 cm below the mucosal junction with the stomach, there was a longitudinal split which was 3.2 cm long.

and extended up the esophagus. Only the upper centimeter of this tear extended entirely through the muscular wall. There was no diverticulum, ulceration or kinking of the esophagus.

Microscopic study showed that the epithelium was moderately thickened throughout. There was no cornification or ulceration. The rupture did not involve an old ulceration or defect in the muscular wall. The edges of the tear were covered with pseudomembrane. Acute infection and hemorrhage had spread from the tear a long distance in the adventitia, in the intermuscular septum and especially in the submucosa, where the phlegmon had reached the middle portion of the esophagus. The spread of hemorrhage and infection had stopped abruptly at the junction with the stomach. In the neck of the cardiospasm there was patchy hemorrhage in the circular muscle. There was also necrosis of portions of muscle which were involved in the phlegmon. An extremely small amount of old fibrosis was present in the strands of muscular fibers near the cardia. Both muscular layers were thickened throughout the entire esophagus, and the circular muscle had attained a thickness of 3.5 mm. The elastic tissue was about normal everywhere, although the circular fibers were relatively more prominent in the sac than elsewhere. Although the ganglion cells were normal in the adjoining stomach, they had practically disappeared in the myenteric plexus of the esophagus. Only three ganglion cells were observed in twenty-three segments of the myenteric plexus. In the lower half of the esophagus the ganglions were involved in the infection which had spread from the rupture, in the upper half the ganglions exhibited much proliferation of supporting cells but were not infected. Sections of the vagus nerve were normal.

CASE 8—A man aged 50 had complained of dysphagia and regurgitation, with increasing emaciation, for two years. He had uremic symptoms when he arrived at the clinic. A stomach tube was passed, but he became irrational and pulled it out. He failed rapidly and died a few days later.

Besides the dilatation and hypertrophy of the esophagus, necropsy revealed bilateral bronchopneumonia, with a small abscess on the right side, a hemangioma of the left vocal cord, an old healed duodenal ulcer, cholelithiasis, cholecystitis and dilatation of the gallbladder, Meckel's diverticulum, melanosis coli, advanced arteriosclerosis, old healed tuberculosis of the spleen, liver and lungs, and arteriosclerotic renal changes.

Examination of the esophagus revealed that the dilatation began abruptly 2 cm above the junction of the gastric and the esophageal mucosa. The sac, which had a circumference of 7 or 8 cm throughout most of its length, extended to the cricoid cartilage, which was 26 cm above the cardia. The lower part of the sac had thick muscular walls while the upper 8 cm of the sac showed thinning of both the mucosal and the muscular layer. In the lower part of the sac there were numerous thickened plaques in the epithelium, which produced a pebbled-leather appearance (fig 7). In the lowest 5 cm of the esophagus there was ulceration between the islands of epithelial thickening. Just above the neck of the cardiospasm one such ulcer had penetrated almost to the adventitia. There was no diverticulum or evidence of kinking or twisting of the esophagus.

Microscopic study showed a general thickening of the esophageal epithelium. Between the plaques of thickened epithelium in the lower part of the esophagus there was acute necrotic and ulcerative inflammation, with many polymorphonuclear leukocytes, which involved the mucosa and submucosa. The muscular layer was thickened in the lower portion of the sac. There was thinning of the circular muscle in the upper part of the sac, with vacuolar degeneration of the muscle fibers but no fibrosis. Circular elastic fibers were relatively more

prominent in the upper part of the sac. The ganglion cells generally had disappeared, only two were seen in eight segments of the myenteric plexus. Their place was taken by some proliferation of the supporting cells. No sections of the vagus nerve could be obtained.

CASE 9—A woman aged 39 had suffered from epigastric pain, vomiting and dysphagia for nineteen years. She had undergone frequent dilation for cardiospasm from 1914 to 1918. A roentgenogram, which was made in 1918, showed both a dilated esophagus and a duodenal ulcer. She returned to the clinic and



Fig 7—Esophagus (case 8) showing the plaques of epithelial thickening mingled with ulceration just above the cardia

underwent further dilations on Jan 3, 1925, Nov 5, 1925, and March 31, 1926. The last operation was followed by epigastric pain and bloody emesis. The following day, dulness was noted at the base of the lungs, especially on the left side. During the next few days five aspirations were performed for empyema of the left pleura, and from 300 to 1,000 cc of fluid was removed at each aspiration. The patient died on April 10, 1926.

Necropsy revealed that rupture of the esophagus had been followed by mediastinitis and empyema on the left side, which had collapsed the lung completely. There also were fibrinous pleuritis at the base of the right lung, a healed duodenal

ulcer, fatty changes in the myocardium and liver, infarcts in the spleen and left kidney and gas bubbles and hemolysis in the submucosa of the colon from which *Clostridium Welchii* was isolated

Examination of the specimen showed that the neck at the cardia, which had a circumference of 3.9 cm, was dilated gradually to a relatively small sac, 16 cm in length and 5.5 cm in circumference. Beginning 2 cm above the mucosal junction and extending upward 5.2 cm was a complete tear through the esophagus. In the middle of the sac the epithelium was dark and lusterless and had the appearance of infarction. There was no diverticulum, scarring, evidence of a twist or kink or hypertrophy of the sphincter or oblique muscle at the cardia.

Microscopically the epithelium showed merely a hyperplastic downward growth of the basal layers, except in regions (as around the rupture or in the middle of the sac) in which the epithelium was lost in acute esophagitis. Sections from the borders of the rupture demonstrated that both mucosa and musculature originally had been normal where the tear occurred. The edges of the tear were covered with pseudomembranous inflammation. Above the rupture, in the middle of the sac, the layers of the esophagus were completely disorganized. The whole wall was a mass of necrotic tissue, hemorrhage and inflammation. Even the myenteric plexus could not be recognized definitely enough to permit the ganglion cells to be counted. Outside the infarcted region the muscular layer appeared normal, except for a slight increase in the fibrous tissue and circular elastic tissue near the cardia. Six segments of myenteric plexus from parts of the esophagus unaffected by the acute infarction showed only one ganglion cell. The ganglions showed some increase in the number of nuclei of the supporting cells. No sections of the vagus nerve could be obtained.

CASE 10—A man aged 31 had suffered a sudden onset of epigastric pain and regurgitation four years before he came to the clinic. The gallbladder and appendix had been removed elsewhere, without relief. Since that time there had been increasing dysphagia, regurgitation and loss of weight. On his trip to the clinic he had become mentally confused. Shortly after his arrival he became acutely maniacal. Examination was impossible. He was sent to the state hospital, where he died seven days later.

At necropsy a diagnosis was made of dilatation of the esophagus, emaciation, toxic psychosis (possibly the result of hunger and dehydration), exhaustion, edema and congestion of the brain and old healed tuberculosis of the lungs and lymph nodes.

Examination showed that the esophagus, which was normal in size at its lower extremity, was dilated gradually to a fusiform sac with a maximal circumference of 11 cm at a point 10 cm from the cardia. The epithelium was generally thickened. In the lower part of the sac were several small papillomatous protrusions of the mucous membrane, which averaged 2 mm in diameter. The muscular layer of the esophagus was relatively thin. There was no ulceration, diverticulum or evidence of a twist or kink in the esophagus or of hypertrophy of the oblique muscle.

The epithelium was normal microscopically, except for some thickening. One section near the cardia, however, passed through the scar of a healed ulcer. This old ulcer, which was not recognized grossly, had once extended down to the circular muscle. The muscular layer appeared normal and did not exhibit any fibrosis. The number of circular elastic fibers was markedly increased in the sac. The ganglion cells had mostly disappeared from the myenteric plexus, only three cells being seen in fifteen segments. The ganglion cells had been replaced

by a proliferation of supporting cells, which frequently appeared in the form of whorls, which I have labeled glomeruloids. Sections of the vagus nerve appeared normal.

CASE 11—A man aged 62 first came to the clinic in 1921, because of stomach trouble, which had been present for three years. A diagnosis of cardiospasm was made and dilation relieved the symptoms. He returned frequently between 1923 and 1929, because of chronic arthritis. From March 21 to April 25, 1929, several casts were applied to his knees for wedging. There was no manipulation of the joints, however. On April 29 the patient suddenly fell unconscious in a convulsion. He revived for a few minutes and then collapsed and died.

Necropsy did not solve satisfactorily the question of the cause of death. The observations included chronic pulmonary tuberculosis, healed tuberculosis of the spleen and liver, chronic arthritis and moderate arteriosclerosis. The brain was normal.



Fig 8—Section of the esophagus, $\times 16$, near the cardia (case 11). At the extreme upper right is an island of thickened epithelium. That this thickness is not an artefact resulting from oblique cutting is shown by the fact that the papillae are cut in the direction of their axes. In the upper center is an esophageal gland. Below and to the right of it the muscular wall of the esophagus consists of longitudinal fibers only, the circular muscle apparently has been ruptured in the course of operative dilation.

The lowest 4 cm of the esophagus, which constituted the neck of the dilated esophagus, was of normal size. Above this was a sac which was dilated to a circumference of 85 cm. The mucosa presented numerous islands of thickened epithelium. Twelve centimeters from the cardia was a diverticulum 0.6 cm deep and 1.6 cm across its mouth. There was no scarred lymph node attached to the fundus of the diverticulum. On the outer surface of the sac was one strand of longitudinal muscle which was greatly thickened.

Microscopically the epithelium showed numerous islands of thickening and elongated papillae (fig 8). Occasional polymorphonuclear leukocytes were seen.

in the thickened epithelium. There was no ulceration. At the cardia and in the neck of the cardiospasm the circular muscle had the appearance of having been pulled apart. It was atrophic, the strands were separated, and some sections did not reveal any circular muscle at all. I have mentioned this as a late appearance following successful dilation. In the sac the muscular layers were generally normal, except that the thickened strand of longitudinal muscle, which was mentioned in the gross description, disclosed considerable vacuolar degeneration of the muscle cells. Special staining revealed that the vacuoles did not contain fat. In the walls of the sac the capillaries and small veins were greatly dilated. The amount of circular elastic tissue was relatively increased in the sac. The diverticulum had the appearance of a herniation of the mucosa through the muscular wall of the esophagus. The muscularis mucosae was normal throughout the diverticulum, but the circular muscle was thinned almost to extinction, and the strands of the longitudinal muscle were pushed to the sides. Ganglion cells generally had disappeared throughout the esophagus, only seven were seen in sixteen measured segments of the myenteric plexus. There was little proliferative reaction in the ganglions. Sections of the vagus nerve were normal.

CASE 12—A woman aged 60 had complained of "gas on the stomach" for two years. For seven months before she came to the clinic there had been progressive dysphagia. Administration of belladonna had given transient relief, but the patient had lost 25 pounds (11.3 Kg). When she came to the clinic she was pale, weak and emaciated. She was told to swallow thread for a guide for dilation. At noon on the first day she became dyspneic after eating. A few physical signs were discovered over the lower lobe of the left lung. Despite oxygen therapy, she died the same evening (Nov 8, 1932).

Necropsy revealed edema of the lungs and a limited beginning pneumonia. There was a pedunculated lipoma on the outside of the stomach, near the cardia. A mucocele of the appendix, one gallstone, granular cystitis, moderate arteriosclerosis and healed pulmonary tuberculosis were also present.

A specimen of the esophagus showed more dilatation and more thinning of the wall than were present in any case that I previously had studied (fig 9). The neck, or undilated portion, of the esophagus extended upward 15 cm from the mucosal junction with the stomach. Above this was a sac which measured 25 cm in length and 16 cm in its greatest circumference. The thinning of the wall involved both the muscular and the mucosal layer. A few varicose veins were seen in the submucosa. There was no diverticulum or ulceration or any evidence of a thickened sphincter, hypertrophied oblique muscle or kink in the esophagus at the cardia. The stomach likewise was considerably dilated.

Microscopic examination showed that the epithelium was generally thinned, except for a few islands of localized thickening at the cardia. No ulceration was present. The muscular layers were thinned throughout but more so in the sac than in the neck of the cardiospasm. There was a slight increase in the amount of circular elastic fibers in the neck, but a general thinning of all elastic fibers was noted in the sac. The number of ganglion cells in the myenteric plexus was reduced, only twelve cells were seen in twelve measured segments. The complete vagus plexus, which was examined with many sections and stains, was entirely normal.

CASE 13—A man aged 69 died at the clinic with uremic symptoms on May 22, 1934. At no time had he complained of dysphagia. When his wife was questioned in the light of the postmortem observations, however, she recalled that in his youth the patient had suffered great difficulty in swallowing. He had

vomited with great ease and had found it necessary to sleep with a towel on his pillow and a rug beside his bed on account of regurgitation at night. These symptoms had not troubled him for many years.

Besides the dilated esophagus, necropsy revealed carcinoma of the bladder, which had metastasized to the ureters, liver, lung and lymph nodes, pyelonephritis, chronic tuberculosis of the hilus, lymph nodes and spleen, and hypertrophy of the heart.

The relationship between the cardia and the diaphragm was examined *in situ*, and it was observed that there was room in the esophageal hiatus to slip two fingers



Fig. 9—The esophagus and stomach (case 12) before being opened

between the esophagus and diaphragm. A plaster cast was made of the stomach and esophagus before these organs were opened. The cast was not absolutely continuous between the two organs because the lower end of the cardia was partially occluded by a wad of vegetable fibers. The esophagus was not only greatly dilated but also somewhat stretched lengthwise. As a consequence, there was some bending of the esophagus, but obviously there was not enough kinking to produce obstruction, as the cast demonstrated. Beginning at the cardia, a neck, or undilated portion of the esophagus, extended upward for a distance of 4.5 cm. In this portion the muscular walls were thick, and the mucosa was folded longitudinally. The esophagus then curved to the right and gradually widened into a sac which was 14 cm long and 16 cm in circumference. The mucosal and muscular

walls of the sac were thinned. The epithelium presented numerous ulcers, which were 1 or 2 mm in diameter. About 25 cm above the upper end of the neck was a diverticulum 0.7 cm in depth. Its mouth measured 0.6 cm in its vertical and 1.5 cm in its horizontal diameter. At the upper end of the sac, opposite the

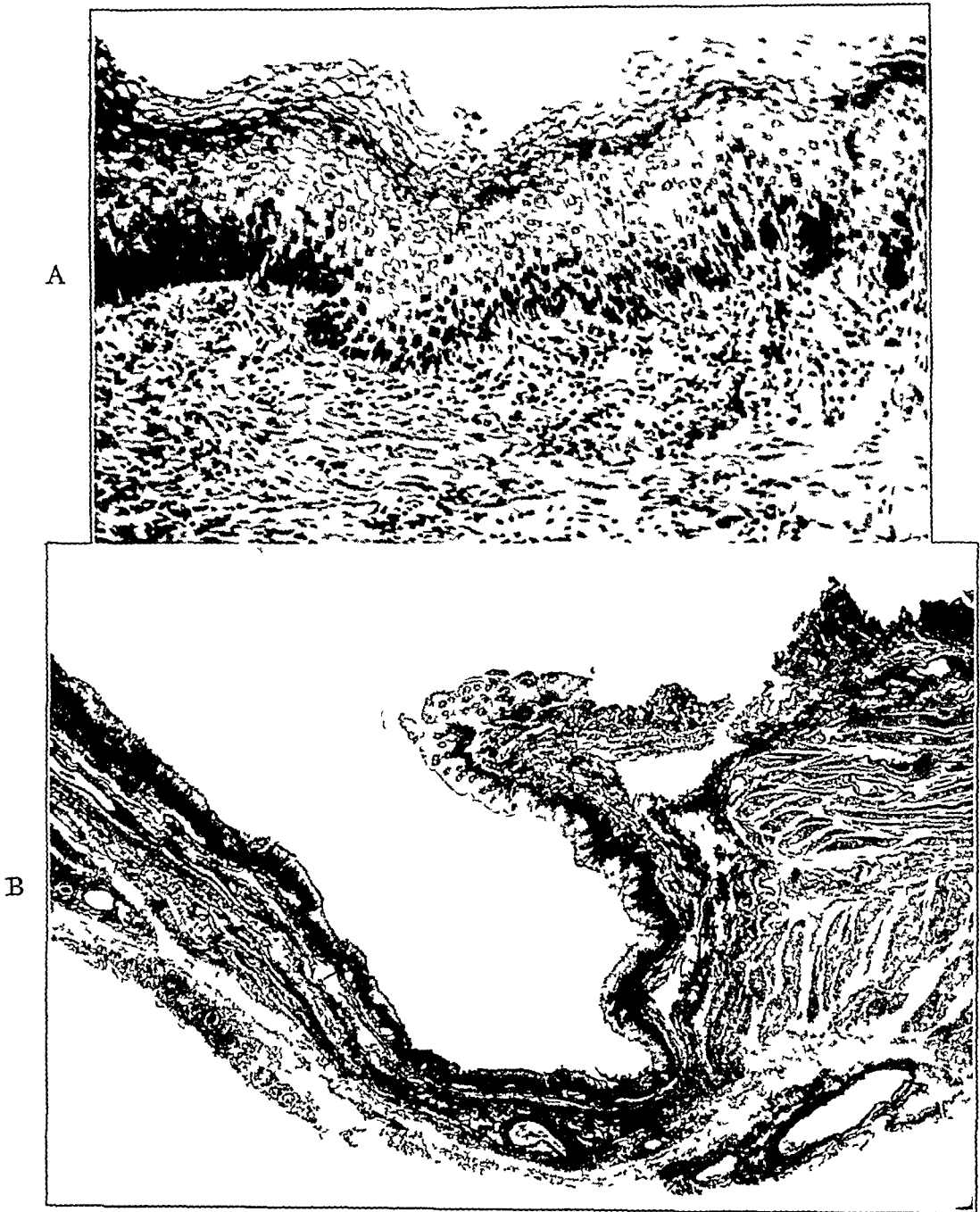


Fig 10—*A*, the epithelium of the esophagus (case 13) showing pathologic cornification, $\times 115$. *B*, a diverticulum of the esophagus (case 13, $\times 10$). On the right may be seen the strands of circular and longitudinal muscle, apparently pushed aside by the pouch, which is lined only with muscularis mucosae.

bifurcation of the trachea, was another undilated portion of the esophagus, which had thick muscular walls. I shall speak of it as the upper neck. It curved to

the left and had a length of 4 cm and a circumference, when opened, of 7 cm. Above this was another thin-walled sac, which reached to the cricoid cartilage. It was 7.5 cm long and 10.5 cm in circumference.

Microscopically the epithelium was thickened throughout. Near the cardia it was somewhat edematous, and above this point it presented beginning cornification of the mucous membrane type (fig 10 A). In the lower neck the muscular layers were much thickened but otherwise were normal and free from fibrosis. In the lower sac there was not only much thinning but also extensive fibrosis of the muscle. In the upper neck the muscle was normal, but much thickened, the circular muscle had a thickness of 6 mm. In the upper sac the muscular layers were thin but otherwise normal. Here, the muscle fibers were largely striated. The elastic fibers were relatively increased in number in the upper and lower necks and at the sites of fibrosis. In the latter situations circular fibers predominated. The wall of the diverticulum resembled that in the eleventh case, in that the longitudinal fibers appeared to be pushed apart, the circular fibers were thinned to extinction and only the muscularis mucosae was present in the fundus of the diverticulum (fig 10 B). Ganglion cells had disappeared throughout the esophagus, no cells were seen in nineteen measured segments of the myenteric plexus. Practically no proliferative changes were evident in the ganglions. Sections of the vagus nerve were normal.

COMMENT

The details of the clinical findings in these cases are shown in table 2. The conclusions which may be drawn from them have no small importance.

In all cases the dilated portion of the esophagus, or sac, was separated from the stomach by an undilated segment of esophagus, which I have labeled the neck. The neck varied in length between 1.5 and 4.5 cm. In no case was there organic narrowing of the neck or scarring in or around it. Accordingly, one may lay the ghost of Mosher's "fibrosis of the terminal esophagus." In no case was there evidence of a thickened sphincter or of a hypertrophic oblique muscle of the stomach. "Kinking of the terminal esophagus" was certainly absent in all cases of early moderate dilatation. Kinking of the esophagus can evidently occur only in cases of very old cardiospasm in which there has been lengthening as well as dilatation of the esophagus. Accordingly, it probably can be eliminated as an etiologic factor. No evidence could be found for compression of the esophagus by spasm of the diaphragm. The absence of hepatomegaly and of any pathologic condition in the liver in this and other series of cases of cardiospasm speaks strongly against "pressure of the liver tunnel" as a cause of the dysphagia. Finally, the theory which invokes "the pressure of the lung tips" can be eliminated by an appeal to simple physics—the lungs are elastic and do not press against but tend to pull away from the parieties.

In ten of the thirteen cases in which adequate sections could be obtained the vagus nerve was entirely normal. In every case, however, there was a striking loss or complete absence of ganglion cells from the

myenteric plexus Only seventy-four cells were seen in a total of 233 segments of the myenteric plexus, which were 1 cm in length This loss was frequently accompanied with a proliferation of the supporting cells of the ganglions Sometimes there was a picture which I have interpreted as a mass of new proliferative supporting cells filling the old capsule of an extinct ganglion cell I have termed this appearance a glomeruloid Sometimes there was actual inflammation in and about the ganglions In some cases there was nothing to be seen except simple absence of ganglion cells from the ganglions

TABLE 2—Data for Thirteen Cases of Cardiospasm

Case	Sex	Age, Years	Duration of Symptoms, Years	Operative Dilatation	Rupture of Esophagus	Cause of Death	Divericulum of Esophagus	Peptic Ulcer	Maximal Circumference of Sac (Fixed), Cm	Thickness of Muscle in Sac
1	M	53	5	+	0	Unknown (cardiac?)	0	Gastric	8	Normal
2	F	29	2	+	+	Cellulitis of neck	0	0	5.4	Increased
3	F	39	17	+	+	Empyema on left	0	0	?	Increased
4	M	17	11+	0	0	Unknown	0	0	8	Increased
5	F	66	3	+	+	Bilateral empyema	0	0	8	Increased
6	F	8	3	0	0	Inanition	0	0	7.5	Increased
7	M	58	20	+	+	Empyema on left	0	0	5.6	Increased
8	M	50	2	0	0	Inanition and pneumonia	0	Healed duodenal ulcer	7.5	Increased
9	F	39	19	+	+	Empyema on left	0	Healed duodenal ulcer	5.5	Decreased
10	M	31	4	0	0	Toxic psychosis	0	0	9	Normal
11	M	62	11	+	0	Unknown	+	0	8.6	Irregular
12	F	60	2	0	0	Unknown (edema of lungs?)	0	0	16	Decreased
13	M	69	30+	0	0	Carcinoma of bladder	—	0	16	Decreased

In may be argued that the loss of ganglion cells is secondary to pressure in the dilated sac It is to be pointed out, however, that the loss of ganglion cells is equally great in the undilated neck at the cardia Furthermore, it should be pointed out that in most of these cases the circumference of the sac was only about twice the circumference of the normal esophagus Accordingly, the increased mean distance between ganglion cells can account for a reduction of only about 50 per cent in the number of cells in the sac

My results are compatible with the theory of Hurst,⁷¹ namely, that cardiospasm or achalasia of the cardia, is primarily a disease of the myenteric plexus. Hurst expressed the opinion that with the destruction of the myenteric plexus the sympathetic fibers to the terminal portion of the esophagus are allowed to act unopposed. As a result, the terminal portion of the esophagus does not relax normally with the swallowing reflex, and dysphagia results.

The varying anatomic pictures in these thirteen cases can best be explained by introducing the conception of "compensated" and "decompensated" cardiospasm. In early and moderate cardiospasm the esophagus responds to the obstruction in a characteristic fashion. It dilates only slightly. Instead, the muscular walls, and especially the circular muscle, are greatly thickened. The thickness of the circular elastic fibers also is relatively increased in response to the increased pressure within the esophagus. The epithelium also is thickened uniformly but does not become ulcerated. Case 2 furnishes an excellent example of such a compensated cardiospasm.

If the long-continued and severe pressure from within, however, overcomes the resistance of the esophagus to dilatation, certain other changes occur. The esophagus becomes prodigiously dilated and also stretched lengthwise, so that bends and kinks may occur. The muscle, instead of being thicker than normal, is thinned. The muscular fibers in the sac may show vacuolar changes or even extensive fibrosis (case 13). Also, the elastic tissue of the esophagus is thinned out. There may be dilatation of the capillary venules as a result of obstruction to the venous return. The mucosa may herniate through the muscular wall in the form of a diverticulum (cases 11 and 13). The epithelium may show beginning cornification or plaques of great thickening or ulceration. In case 13 is presented a typical picture of decompensated cardiospasm. Most of the anatomic features in these thirteen cases can be regarded as representing various stages of compensation. The chronically infected esophagus in case 6 and the completely atonic esophagus in case 12 are somewhat atypical but may fit into the same scheme.

It is now necessary to consider the effect of operative dilation on the cardia. In most of these cases rupture of the esophagus complicated the picture. In case 11, however, operative dilation of the cardia, years previously produced complete relief of symptoms. In this case the fibers of the circular muscle in the neck of the cardiospasm were pulled apart in a way that points to an old submucous rupture of the circular muscle. This same frayed appearance of the circular muscle was present after recent dilation in case 3.

71 Hurst, A. F. (a) The Treatment of Achalasia of the Cardia (So-Called "Cardiospasm") *Lancet* 1 618-619 (March 19) 1927, (b) Some Disorders of the Esophagus, *J. A. M. A.* 102 582-587 (Feb. 24) 1934.

In case a rupture through the wall of the esophagus is produced by operation, certain characteristic observations are made. In case 2, in which dilation was performed elsewhere, the esophagus had been punctured high in the cervical region, apparently with some pointed instrument. Cases 3, 5, 7 and 9, however, in which the rupture followed the use of the Plummer dilator, were markedly similar. The tear was always longitudinal. It was always through a normal mucous membrane and muscular wall. In three cases it produced only empyema on the left side, and in the one case, in which bilateral empyema was produced, the rupture was on the left side of the esophagus. The tear was either entirely above the juncture with the mucous membrane of the stomach (in three cases) or almost entirely above the juncture (in one case). The rupture was always followed by a rapidly spreading inflammatory reaction of great violence.

One more point remains to be considered. In cases 1, 4, 11 and 12 death occurred suddenly and could not be explained satisfactorily by the postmortem observations. I should not care to defend the thesis that the sac in a case of cardiospasm may exert such pressure on the mediastinal structures as to be the cause of sudden death, yet this possibility is worthy of consideration.

Progress in Internal Medicine

DISEASES OF METABOLISM AND NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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II NUTRITION

By DR WILBUR

Although the symptomatic and, to some extent, the pathologic results which accompany states of marked deprivation of vitamins have been largely described, great interest has been shown in the past year in the early alterations in normal physiologic processes which occur before these gross pathologic changes have become manifest. In fact, chief interest in the field of nutrition is at present directed toward studies of the metabolic influences of the various vitamins. Of particular interest to clinicians have been methods of recognition and treatment of states of moderate and mild vitamin deficiency, the effect of abnormalities in gastro-intestinal function in the production or conditioning of disease due to vitamin deficiency, studies of the metabolism of vitamin C and, lastly, studies of the physiologic properties of the vitamin B complex, elucidation of the components of which has advanced steadily.

VITAMIN A

The daily requirement of vitamin A is still unknown. Indeed, it probably will be many years before the requirement of vitamin A or of any of the other vitamins can be clearly established. The difficulty in expressing in exact figures the requirement of any vitamin is realized when one considers the influences of absorption, storage and destruction and the variability in minimal and optimal requirement. Perhaps eventually the quantitative requirement will be stated, as it now is for protein, to lie between certain minimal and optimal levels. This tendency has already received expression in the report of a cooperative committee appointed by the Council on Pharmacy and Chemistry and the Committee (now Council) on Foods,¹ both of the American Medical Association.

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The section on "Diseases of Metabolism" was published in the February issue of this journal.

1 The Status of Certain Questions Concerning Vitamins, report of the Council on Pharmacy and Chemistry, J A M A **106** 1732-1735 (May 16) 1936

This committee has recommended for approval for lay advertising any cod liver oil or preparation containing vitamin A if the prescribed daily dose provides at least 6,250 and not more than 10,000 U S P units of vitamin A. This is the vitamin content provided by 2 teaspoonfuls of cod liver oil, which meets the standard given in "New and Non-official Remedies" (1936). The committee noted a lack of data on the basis of which to determine the dose of vitamin A for adults, although Harris² placed the minimal requirement at about 1,000 U S P units daily. The requirement of children per kilogram of body weight is greater than that of adults, because of the processes of growth.

By healthy subjects vitamin A and its precursor, the yellow pigment carotene, are absorbed without difficulty. Evidence gradually has accumulated to show that absorption of vitamin A and carotene may be influenced by a variety of pathologic and perhaps physiologic processes and that under many circumstances the absorption of carotene is more often interfered with than is that of the vitamin itself. It has been suggested that whenever interference with the digestion or absorption of fat occurs, there may be failure in absorption of vitamin A or carotene. In this respect interesting studies have been reported in the past year on the rôle of bile in the utilization of vitamin A. The indispensability of bile in absorption of lipids and the fat-soluble character of the vitamin suggest that, in the absence of bile, there might be serious interference with absorption of vitamin A. However, studies of Schmidt and his associates³ have indicated that absorption of vitamin A of cod liver oil from the gastro-intestinal tract of the rat does occur in the absence of bile, as indicated by studies of vaginal smears as a criterion of deficiency. In contrast, it was found that the rat suffering from deficiency of vitamin A did not respond to oral administration of alpha carotene and beta carotene in the absence of bile. Response occurred, however, when the carotene was administered subcutaneously by injection or when it was administered orally, together with bile acids. In a somewhat related study Altschule⁴ recorded his observations of 11 infants in whom the bile duct was observed post mortem to be congenitally atretic. All the infants had received an adequate diet and had failed to present clinical evidence of vitamin A deficiency. However, in tissues of 6 of the 11 were microscopic changes similar to those

2 Harris, L. J. A Programme for Nutrition Surveys, *Lancet* **1** 966-968 (April 25) 1936.

3 Greaves, J. D., and Schmidt, C. L. A. On the Absorption and Utilization of Carotene and Vitamin A in Choledochocolonostomized Vitamin A Deficient Rats, *Am J Physiol* **111** 492-501 (April) 1935. Schmidt, W., and Schmidt, C. L. A. The Relation of Bile to the Intestinal Absorption of Vitamin A in the Rat, *Univ California Publ, Physiol* **7** 211-221, 1930.

4 Altschule, M. D. Vitamin A Deficiency in Spite of Adequate Diet in Congenital Atresia of the Bile Ducts and Jaundice, *Arch Path* **20** 845-856 (Dec) 1935.

Wolbach and Howe⁵ have described in vitamin A deficiency Altschule said he considered this as evidence that vitamin A had not been absorbed in adequate amounts because of the absence of bile. Consideration must also be given in this connection to the relation of the damaged liver to storage and metabolism of vitamin A.

That infections may influence intestinal function, and particularly absorption, has long been recognized. Heymann's⁶ interesting studies disclosed that 70 per cent of ingested carotene was absorbed by normal infants, whereas if the infants harbored infection of any type, only 36 per cent was absorbed. Heymann expressed the belief that low absorption is not attributable to fever only, since the effect persisted for two weeks beyond the duration of the fever. Heymann could find no evidence that it was attributable to inhibition of absorption of fat and ascribed it to an unknown toxic effect. In the presence of celiac disease, in which absorption of fat is greatly interfered with, vitamin A deficiency has been reported by Friderichsen,⁷ even though vitamin A was given in sweet milk. When the infant under his observation was given mother's milk, immediate improvement resulted. Heymann also has studied a patient with celiac disease who showed complete lack of absorption of vitamin A. Evidence which is interpreted as indicating interference with absorption of vitamin A in pregnancy has been reported by Edmund and Clemmesen.⁸ Thirteen of 20 pregnant women presented night blindness which was relieved in from seven to ten minutes by intramuscular injection of a preparation containing 15,000 U S P units of vitamin A in each cubic centimeter.

Further evidence of the importance of the liver in metabolism of vitamin A is demonstrated by the studies of Heymann⁹ and of Ralli, Pariente, Brandaleone and Davidson.¹⁰ Heymann reported that after cessation of administration of carotene in oil, diabetic patients failed

5 Wolbach, S. B., and Howe, P. R. Tissue Changes Following Deprivation of Fat-Soluble A Vitamin, *J. Exper. Med.* **42** 753-777 (Dec.) 1925.

6 Heymann, W. Absorption of Carotene, *Am. J. Dis. Child.* **51** 273-283 (Feb.) 1936.

7 Friderichsen, C. Quantitative Investigations of the Resorption of A Vitamin in a Case of Coeliakie. Studies of Hypovitaminosis-A, *Acta pædiat.* **18** 377-391, 1936.

8 Edmund, C., and Clemmesen, S. On Parenteral A Vitamin Treatment of Dysaptatio (Nyctalopia-Hemeralopia) in Some Pregnant Women, *Acta med. Scand.* **89** 69-92, 1936.

9 Heymann, Walter. Carotenemia in Diabetes, *J. A. M. A.* **106** 2050-2052 (June 13) 1936.

10 Ralli, Elaine P., Pariente, A. C., Brandaleone, H., and Davidson, S. Effects of Carotene and Vitamin A on Patients with Diabetes Mellitus. III. The Effect of the Daily Administration of Carotene on the Blood Carotene of Normal and Diabetic Individuals. *J. A. M. A.* **106** 1975-1978 (June 6) 1936.

to show the normal decline in the carotene content of the serum, the concentration remained elevated or even increased for from ten to fourteen days after administration had been discontinued. Ralli and his associates reported that the ability of the liver of diabetic patients to convert carotene to vitamin A is diminished and that this leads to increased concentration of carotene in the liver, which in turn interferes with the absorption of carotene from the blood. The evidence indicates that the carotenemia of diabetic patients is not attributable solely to the large carotene content of the diet.

It has long been recognized that vitamin A deficiency is manifested chiefly by an effect on epithelial tissues. It was suggested by Mellanby¹¹ in 1934 that the primary effect of vitamin A deficiency is on nerve tissues and that the epithelial changes may be secondary, attributable to interference with or loss of trophic influences. Although certain changes in the nervous system of animals deprived of vitamin A have been described, such as those recently described by Zimmerman and Cowgill,¹² the conception of Mellanby remains unproved. In an attempt to support this hypothesis by experimental means, King¹³ cut the inferior dental nerves of dogs. This accelerated the rate of growth of the teeth but failed to produce defects such as those observed in the teeth and gums of dogs suffering from vitamin A deficiency. That the results he obtained were attributable to damage of the vasomotor fibers is indicated, since the changes observed were reproduced by section of the cervical sympathetic nerve.

Further attempts to find practical value in the relation of vitamin A to epithelial tissues have led to the use of the vitamin to aid in the healing of wounds and in the treatment of epithelial lesions. Most of the reports of this work have appeared in the foreign literature. Proto¹⁴ and Sandor¹⁵ have reported favorable results. Proto stated that in experimental wounds of rabbits local applications of vitamin A greatly and favorably influenced healing. Concerning the treatment in man of large superficial wounds or of areas from which skin had been excised, Sandor reported favorably on the effect of an ointment or oil.

11 Mellanby, E. Xerophthalmia, Trigeminal Degeneration and Vitamin A Deficiency, *J Path & Bact* **38** 391-407 (May) 1934.

12 Zimmerman, H. M., and Cowgill, G. R. Lesions of the Nervous System in Vitamin Deficiency. IV. The Effect of Carotene in the Treatment of Nervous Disorders in Rats Fed a Diet Low in Vitamin A, *J Nutrition* **11** 411-423 (May) 1936.

13 King, J. D. Dietary Deficiency, Nerve Lesions and the Dental Tissues, *J Physiol* **88** 62-76 (Oct) 1936.

14 Proto, M. Action of Vitamins on Healing of Wounds, *Ann ital di chir* **15** 1-174 (Jan-Feb) 1936, abstr, *J A M A* **107** 627 (Aug 22) 1936.

15 Sandor, Stephan. Vitamin A in the Local Treatment of Wounds, *Lancet* **2** 738-740 (Sept 26) 1936.

containing 2 000 U S P units of vitamin A in each cubic centimeter. Of considerable interest is the report of Lustig and Wachtel¹⁶ on experiments with vitamin A in treatment of cutaneous epitheliomas and mammary carcinomas. After using a preparation containing 40,000 biologic units of vitamin A in each cubic centimeter applied as compresses and injection subcutaneously along with a colloidal copper preparation these investigators reported that the involved area became smaller. New epithelium grew in from the periphery, and the bases of the ulcers became clear. No effect was noted on distant metastatic growths. While Lustig and Wachtel admitted that the treatment was palliative since cures had not occurred, nevertheless they said they were inclined to continue their study and felt that perhaps the use of vitamin A would prove an adjuvant in the treatment of the lesions. Failure of massive doses of carotene in oil administered to rats to influence implanted sarcomatous tumors has been reported by Sure, Buchanan and Thatcher.¹⁷

The relation of vitamin A to genito-urinary function has received further study in the past year. Higgins¹⁸ has continued his studies on urinary calculi associated with vitamin A deficiency. He reported 35 cases in which stones had undergone solution and stated that in his experience since 1932 the incidence of recurring stones following operation has been reduced from 16.4 to 4.7 per cent. Lazarus and Rosenthal,¹⁹ however, have failed to be convinced of the efficacy of the high vitamin acid ash diet, either as a means of dissolving stones or as an absolutely certain means of preventing recurrences. They were unable to explain their failure to reproduce Higgins' results, although failure to treat patients over a sufficiently long period of time may have been a factor. In this connection the report of the cooperative committee,¹ previously noted, is of interest for it is stated that "there is at the present time inadequate evidence to warrant the claim that the ingestion of sufficient vitamin A will prevent the formation of renal calculi in man."

16 Lustig, B., and Wachtel, H. Therapeutic Experiments with Vitamin A in Cancer, *Ztschr. f. Krebsforsch.* **44** 53-58, 1936, abstr., *J. A. M. A.* **107** 1261 (Oct. 10) 1936.

17 Sure, B., Buchanan, K. S., and Thatcher, H. S. Vitamin A and Carcinogenesis. *Am. J. Cancer* **27** 84-86 (May) 1936.

18 Higgins, C. C. Urinary Lithiasis. Experimental Production and Solution with Clinical Application and End-Results, *J. Urol.* **36** 168-177 (Aug) 1936.

19 Lazarus, I. A., and Rosenthal, A. A. Renal Lithiasis—A Resume of Its Present Status and a Preliminary Report on the Vitamin "A" Acid Ash Diet Based upon One Hundred and Twenty-One Private Cases, *Urol. & Cutan. Rev.* **40** 1-8 (Jan) 1936.

The effect of deprivation of vitamin A on the vaginal mucosa has long been recognized, and the effect on the vaginal mucosa of the rat has been used as a measure of vitamin A sufficiency or insufficiency. Coward, Cambden and Lee²⁰ have reported that as a means of quantitative estimation of vitamin A, the method appears to be somewhat less accurate than determination of increase in weight in three weeks of female rats which have been given daily doses of vitamin A after they have ceased to grow on a diet deficient in that factor. Simpson and Mason²¹ have studied the relation of senile vaginitis in human beings to vitamin A deficiency. In 30 cases, in many of which the subjects had been receiving an inadequate diet, an increased oral intake of vitamin A, in cod liver oil or halibut liver oil, proved to be an unusually effective method of producing rapid relief of symptoms and of gross and histologic repair of the vaginal lining.

The relation of vitamin A to resistance to infection has long been a matter of debate. The vitamin has certainly not been shown to be specific in the prevention of colds, influenza and such infections nor has it been demonstrated that ingestion of vitamin A in amounts far in excess of those readily obtained from a properly selected diet is an aid in preventing infections. Mackay and her associates²² have contributed an interesting but not conclusive study in this respect on the therapeutic value of vitamins A and D in measles. In a group of 697 children less than 13 years of age these investigators failed to find any favorable effect on the fatality rate or on the incidence of pneumonia, otorrhea and all other complications, including cutaneous lesions while the patients were in the hospital. Moreover, the duration of pyrexia or length of stay in the hospital was not affected. To children of one group was given 3,000 U S P units of vitamin D daily, to those of another group this dose of vitamin D plus the vitamin A equivalent of 22.5 cc of cod liver oil daily and to those of a third group no vitamin supplements. The negative results may have been attributable to the short time of administration of the vitamins or to the fact that treatment was started too late (81 per cent about the fourth day or later in the disease).

Recognition and Frequency of States of Vitamin A Deficiency—
Recognition of states of marked deprivation of vitamin A is not difficult

20 Coward, Katharine H., Cambden, Marjorie R., and Lee, Eva M. The Determination of Vitamin A by Means of Its Influence on the Vaginal Contents of the Rat, *Biochem J* **29** 2736-2741, 1935

21 Simpson, J. W., and Mason, K. E. A New Concept of Senile Vaginitis, *Am J Obst & Gynec* **32** 125-128 (July) 1936

22 Mackay, Helen M. M., Linford, Hilda M., Mitman, Maurice, and Wild, Marv H. The Therapeutic Value of Vitamins A and D in Measles, *Arch Dis Childhood* **11** 127-142 (June) 1936

if one keeps in mind lesions involving the eyes and the skin. Excellent summaries of the manifestations of vitamin A deficiency have been made by Sweet and K'ang²³ and by Loewenthal²⁴. It seems obvious that these conditions of marked deficiency are rare in the United States, and consequently most attention has been directed toward the much more important problems of the means of recognizing states of mild deficiency. In this connection the work of Jeans and Zentmire,²⁵ first reported in 1934, has been outstanding, and further confirmation of the value of their photometric method of recording impaired visual adaptability to darkness has been reported by them as well as by Frandsen,²⁶ in Denmark. This or some similar simple method seems to be of much value in clinical work, although as yet the limitations of such methods as tests of vitamin A deficiency have not been determined.

Youmans,²⁷ in an excellent summary of methods of recognizing vitamin deficiencies in practice, has emphasized the types of ocular and cutaneous symptoms, signs and tests which may be of value in states of vitamin A deficiency. Ocular symptoms, including asthenopia, poor vision, photophobia, Bitot's spots, conjunctival complaints, dryness and granular appearance of the bulbar conjunctiva when the eyelids are held open for a few minutes, are all signs that arouse suspicion but are inconclusive. Smears of conjunctival or nasal scrapings containing keratotic cells have been described by Blackfan and Wolbach,²⁸ and Sweet and Klang have given further objective evidence. Further confirmation lies in the use of some test, such as the test of adaptability to darkness, of Jeans and Zentmire. Friderichsen has described a method which may overcome some of the objections to the test of Jeans and Zentmire. This depends entirely on objective changes, the observer measures the faintest light which will provoke an oculomotor reflex. Cutaneous evidence of vitamin A deficiency, well described by Frazier

23 Sweet, L. K., and K'ang, H. J. Clinical and Anatomic Study of Avitaminosis A Among the Chinese, *Am J Dis Child* **50** 699-734 (Sept) 1935

24 Lowenthal, L. J. A. The Manifestations of Vitamin A Deficiency in Man, *Ann Trop Med* **29** 407-413 (Dec 18) 1935

25 Jeans, P. C., and Zentmire, Zelma. A Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency, *J A M A* **102** 892-894 (March 24) 1934

26 Frandsen, Helga. Hemeralopia as an Early Criterion of A-Avitaminosis and Clinical Symptoms and Treatment of This Disease, *Acta ophth, supp* **4**, 1935, p 7-160

27 Youmans, J. B. The Present Status of Vitamin Deficiencies in Practice, *J A M A* **108** 15-20 (Jan 2) 1937

28 Blackfan, K. D., and Wolbach, S. B. Vitamin A Deficiency in Infants. A Clinical and Pathological Study, *J Pediat* **3** 679-706 (Nov) 1933

and Hu²⁹ and by Loewenthal,³⁰ consists of a fairly characteristic keratotic papular lesion of varying size occurring especially on the thighs and extensor surfaces of the arms and legs. It is more common among adults than children and involves principally pilosebaceous follicles. A somewhat similar lesion, occurring in the presence of vitamin C deficiency, has been reported by Scheer and Keil.³¹

The presence of one or more of the foregoing signs might constitute good presumptive evidence of vitamin A deficiency, and this presumption would be greatly strengthened by the disappearance of the noted symptoms and signs following administration of pure vitamin A. However, the therapeutic test does not as yet constitute proof, for this, quantitative objective data will be required.

Because of the variability, and in some instances unreliability of methods of determining mild states of vitamin A deficiency, the frequency of such deficiency states is not clearly established. As a result of their studies, Jeans and Zentmire³² offered evidence that in Iowa 26 per cent of a group of rural school children and 53 per cent of a group of village school children were deficient in vitamin A, in a group of urban children the proportion for the higher economic level was 56 per cent, for a middle level 63 per cent and for a low economic level 79 per cent. Park,³³ using the same method, tested 275 patients with a wide variety of diseases and found many with evidences of vitamin A deficiency. Frandsen³⁴ observed slight hemeralopia in 46 of 65 apparently healthy school children in Copenhagen.

VITAMIN B COMPLEX

There is ample chemical and physiologic evidence to indicate that the original water-soluble vitamin B is in reality a complex and consists of several distinct chemical entities. In the past years two factors, one a heat-labile vitamin, B₁, and the other a heat-stable vitamin, B₂, or G, were recognized. Other factors, including vitamins B₃, B₄ and B₅, have been described but not universally recognized. In a recent

29 Frazier, C. N., and Hu, C. K. Cutaneous Lesions Associated with a Deficiency in Vitamin A in Man, *Arch Int Med* **48** 507-514 (Sept.) 1931.

30 Loewenthal, L. J. A. A New Cutaneous Manifestation in the Syndrome of Vitamin A Deficiency, *Arch Dermat & Syph* **28** 700-708 (Nov.) 1933.

31 Scheer, M., and Keil, H. Follicular Lesions in Vitamin A and C Deficiencies, *Arch Dermat & Syph* **30** 177-185 (Aug.) 1934.

32 Jeans, P. C., and Zentmire, Zelma. The Prevalence of Vitamin A Deficiency Among Iowa Children, *J A M A* **106** 996-997 (March 21) 1936.

33 Park, I. O. Preliminary Observations on Vitamin A Deficiency as Shown by Studies with the Visual Photometer, *J Oklahoma M A* **28** 357-364 (Oct.) 1935.

34 Frandsen, H. Investigation of Hemeralopia as Evidence of Minor Degrees of Vitamin A Deficiency, *Nutrition Abst & Rev* **4** 621-622, 1935.

summary of this problem, Peters³⁵ revealed that at least six entities compose the vitamin B complex, as follows

- Vitamin B₁ (aneurin or torulin)
- Vitamin B₂ (G) $\left\{ \begin{array}{l} \text{lactoflavine} \\ \text{vitamin B}_6 \text{ (rat antidermatitis)} \end{array} \right.$
- Vitamins B₃ and B₅ (including the chicken antipellagra factor)
- Vitamin B₄ (position at present obscure)

The relation of these factors to the factors of the human antipellagra (P P) substance, to black tongue of dogs, to heart block of pigeons and possibly to other growth factors is not as yet clear, nor is it evident how many of these, other than vitamin B₁ and perhaps vitamin B₂, are essential for man. The delay in elucidating the nature of and the relation between the various factors is occasioned by the extreme difficulty of the experimental work and the variability in requirements of various test animals.

Vitamin B₁, which has been synthesized, is a pyrimidine thiazole (sulfur-nitrogen-carbon ring) compound, according to Williams³⁶. Lactoflavine, which is one of the components of vitamin B₂ (G), also has been synthesized, it is allied to the purines, pyrimidines and nucleotides and has as its principal component the iso-alloxazine nucleus. The chemical composition and structure of the other components of the vitamin B complex are unknown.

Vitamin B₁—It has been recognized for many years that vitamin B₁ is essential for growth, probably because of its influence in tissue oxidation, particularly in oxidation of carbohydrates. In 1929 Kinnersley and Peters³⁷ produced evidence that there was an increased amount of lactic acid in the brains of pigeons in terminal stages of vitamin B₁ deficiency as compared to that in the brains of normal pigeons. Subsequently Peters and Thompson³⁸ and Sherman and Elvehjem³⁹ revealed the importance of vitamin B₁ in the oxidation of pyruvic acid, in fact, the vitamin appears to be an essential catalyst in

35 Peters, R. A. The Vitamin B Complex, Brit M J **2** 903-905 (Nov 7) 1936

36 Williams, quoted by Peters³⁵

37 Kinnersley, H. W., and Peters, R. A. Observations upon Carbohydrate Metabolism in Birds. I. The Relation Between the Lactic Acid Content of the Brain and the Symptoms of Opisthotonus in Rice-Fed Pigeons, Biochem J **23** 1126-1136, 1929

38 Peters, R. A., and Thompson, R. H. S. Pyruvic Acid as an Intermediary Metabolite in the Brain Tissue of Avitaminous and Normal Pigeons, Biochem J **28** 916-925, 1934

39 Sherman, W. C., and Elvehjem, C. A. In Vitro Studies on Lactic Acid Metabolism in Tissues from Polyneuritic Chicks, Biochem J **30** 785-793 (May) 1936, In Vitro Action of Crystalline Vitamin B₁ on Pyruvic Acid Metabolism in Tissues from Polyneuritic Chicks, Am J Physiol **117** 142-150 (Sept) 1936

the oxidation of pyruvic acid. As Peters and Thompson have pointed out, the extensive evidence for this fact can be summarized by saying that vitamin B₁ can be shown *in vitro* to have a specific catalytic effect on the brain tissue of pigeons suffering from deficiency of this vitamin and that pyruvic acid accumulates in the blood of animals, and probably of man, suffering from deficiency of vitamin B₁. The accumulation of lactic acid in the blood and tissues, which is a marked feature of vitamin B₁ deficiency and of beriberi in man, may be explained by the suggestion that the oxidation of lactic acid is inhibited at the stage of pyruvic acid. These changes in the nervous system probably explain many of the symptoms of vitamin B₁ deficiency, the remaining symptoms may be attributable to the influence of the vitamin on carbohydrate metabolism in tissues other than the brain. The effect of consumption of large quantities of carbohydrate on the requirement of vitamin B₁ has been of particular interest in this respect. Stepp and Schroeder⁴⁰ have reported the first case of relative beriberi in man, attributable to consumption of excessive carbohydrate (in their case from 500 to 1,500 Gm of sugar daily).

Previous evidence suggesting a sparing action of a diet high in fat on the vitamin B₁ requirement has been denied by Sure and Buchanan⁴¹ and by Westenbrink.⁴² Of interest also is the work of Cowgill and Dann⁴³ on the failure of dinitrophenol to influence the vitamin B₁ requirement of dogs. It is generally accepted that elevation of the basal metabolic rate leads to an increased requirement for vitamin B₁. In these studies of Cowgill and Dann the average increase in the basal metabolic rate was 28 per cent, and yet there was no demonstrable effect on the vitamin B₁ requirement, probably because the important factor in determining the requirement of the vitamin is the total and not the basal metabolism.

The daily requirement for vitamin B₁ has been expressed by Cowgill⁴⁴ as about 300 U S P units for a man weighing 70 Kg. Harris

40 Stepp, W., and Schroeder, H. Beriberierkrankung beim Menschen hervorgerufen durch ubermassigen Zuckergenuss, *Munchen med Wchnschr* **83** 763-764 (May 8) 1936

41 Sure, B., and Buchanan, K. S. Avitaminosis. Influence of High Fat-Containing Diets on Vitamin B₁ Requirements, *Proc Soc Exper Biol & Med* **33** 75-76 (Oct) 1935

42 Westenbrink, H. G. K. Physiologic Action of Vitamin B₁, *Nutrition Abst & Rev* **5** 944 (April) 1936

43 Cowgill, G. R., and Dann, Margaret. The Failure of Dinitrophenol to Influence the Vitamin B Requirement, *Yale J Biol & Med* **8** 501-509 (May) 1936

44 Cowgill, G. R. The Vitamin B Requirement of Man, New Haven, Conn., Yale University Press, 1934

and Leong⁴⁵ calculated the requirement as 250 to 500 international units daily (about 1 mg of crystalline vitamin) Baker and Wright⁴⁶ have reemphasized the fact that vitamin B₁ is not abundant in most foods Most fresh foods contain about 1 international unit per gram, but the variability in this factor and the amount of the vitamin destroyed by processing of foods must be taken into consideration in any calculation of the content of the diet It is exceedingly important to recall that during the process of digestion and alimentation there may be destruction or failure of absorption of vitamins and that even though the diet contains an adequate supply, a deficiency state may result Scheunert and Schieblich⁴⁷ have shown, for example, that in dogs with an ileac fistula at least 66.6 per cent of vitamin B₁ administered by mouth (and a considerable amount of vitamin B₂) was absorbed in the stomach or small intestine

A method of corroborating clinical impressions of mild states of vitamin B₁ deficiency may result from studies now in progress on urinary excretion of this vitamin Helmer,⁴⁸ Harris and Leong and Roscoe⁴⁹ have published their results in the past year, and by biologic tests all have found appreciable quantities of the vitamin in urine According to Harris and Leong, the daily output of vitamin B₁ in the urine of 9 healthy adults on "normal" diets amounted to from 12 to 35 international units, with an average of 20 This represented only 5 to 8 per cent of the intake Variations could be noted when the vitamin B₁ content of the diet was increased or decreased, and the conclusion was reached that a daily excretion of less than 12 international units supports the presumption that the diet has less than a normal allowance of vitamin B₁ Roscoe said she was less convinced of the value of the estimation because of the variability in amounts excreted by normal subjects, in fact, in the urine of some, vitamin B₁ appeared not to be excreted in measurable quantities, although the intake was "normal" In addition, when vitamin B₁ was added to the diet in definite amounts, it was excreted by some and retained by other "normal" subjects The vitamin B₁ content of the blood is at present being studied These tests also depend on biologic methods, and in unpublished data Meiklejohn⁵⁰

45 Harris, L. J., and Leong, P. C. Vitamins in Human Nutrition The Excretion of Vitamin B₁ in Human Urine and Its Dependence on the Dietary Intake, *Lancet* **1** 886-894 (April 18) 1936

46 Baker, Audrey Z., and Wright, Margaret D. The Vitamin B₁ Content of Foods, *Biochem J* **29** 1802-1807, 1935

47 Scheunert, A., and Schieblich, M. Ueber die Resorption von Vitamin B um Dummarm, *Nutrition Abstr & Rev* **5** 946 (April) 1936

48 Helmer, O. M. Vitamin B₁ and B₂ Content of Human Urine, *Proc Soc Exper Biol & Med* **32** 1187-1188 (April) 1935

49 Roscoe, Margaret H. The B-Vitamins in Human Urine, *Biochem J* **30** 1053-1063 (June) 1936

50 Meiklejohn, A. P., quoted by Peters³⁵

reported the normal value for man to be 4 international units (85 micrograms \pm 1) for each hundred cubic centimeters of blood

It has long been recognized that deficiency of vitamin B₁ leads to the development of beriberi. However, gradually accumulating evidence indicates that it may be a significant factor in leading to disturbances of the eye, of the nervous system, of the cardiovascular apparatus and of the gastro-intestinal tract and may cause diabetes and edema as well as other symptoms. Of chief clinical interest is the effect on the nervous and cardiovascular systems. Strauss⁵¹ demonstrated clearly the etiologic relationship of vitamin B₁ to so-called alcoholic polyneuritis. Reports from other clinics have substantiated this and have recorded therapeutic value in the administration of large quantities of vitamin B₁ in the treatment of the condition. Jolliffe, Colbert and Joffe⁵² have offered further evidence of this relationship by careful studies of the diets of 42 alcoholic addicts. They demonstrated that in their series the intake of vitamin B₁ of every alcoholic addict who had polyneuritis was estimated to be inadequate (Cowgill's formula), none of the addicts whose intake of vitamin B₁ was estimated as adequate had polyneuritis, and every addict whose intake of this vitamin was estimated as having been absolutely deficient for twenty-one days had polyneuritis. Subsequently, Jolliffe and Colbert⁵³ presented further evidence of the effects of vitamin B₁ in the treatment of "alcoholic" polyneuritis. In studies of a group of chronic alcoholic addicts with uncomplicated polyneuritis who were given diets containing slightly inadequate or barely adequate quantities of vitamin B₁, no improvement was noted in the objective signs of peripheral neuritis over a period of one month. The condition of subjects whose treatment consisted of an intake of vitamin B₁ that was approximately twice their predicted requirement improved but not as rapidly as, or in degree equal to, that of subjects who received four times their requirement of vitamin B₁. It is possible that fractions of the vitamin B complex other than vitamin B₁ were therapeutically significant in these cases, since a preparation of autolyzed brewer's yeast was used. It is particularly interesting in this respect to record the failure of Wechsler, Jervis and Potts⁵⁴ to produce the clinical or pathologic syndrome of polyneuritis in monkeys. Deficient intake, relative and absolute, of vitamin B₁ alone or combined

51 Strauss, M. B. The Etiology of "Alcoholic" Polyneuritis, *Am. J. M. Sc.* **189** 378-382 (March) 1935

52 Jolliffe, N., Colbert, C. N., and Joffe, P. M. Observations on the Etiologic Relationship of Vitamin B (B₁) to Polyneuritis in the Alcohol Addict, *Am. J. M. Sc.* **191** 515-526 (April) 1936

53 Jolliffe, N., and Colbert, C. N. The Etiology of Polyneuritis in the Alcohol Addict, *J. A. M. A.* **107** 642-647 (Aug. 29) 1936

54 Wechsler, I. S., Jervis, G. A., and Potts, H. D. Experimental Study of Alcoholism and Vitamin B Deficiency in Monkeys, *Bull. Neurol. Inst. New York* **5** 453-475 (Aug.) 1936

with acute and chronic alcoholism, did not produce clinical or pathologic features suggesting polyneuritis. Whether this unusual resistance to alcoholic intoxication and vitamin B₁ deficiency represents a species difference is unknown.

Cardiovascular disturbances involving particularly the heart and the capillaries are known to be associated with beriberi and have led to the designation "beriberi heart." This condition, which has been thoroughly described clinically and pathologically by Wenckebach,⁵⁵ is rarely observed in the United States. Recent studies made by Weiss and Wilkins⁵⁶ are of particular interest because an attempt has been made to describe the cardiovascular symptoms and signs of a group of patients who gave evidence of mild and moderate deficiency of vitamin B₁ and to delineate the cardiovascular conditions in which vitamin B₁ may be of therapeutic value. From a group of patients in the Boston City Hospital 97 were selected in whom disturbances of cardiovascular function seemed related to nutritional factors. Patients were selected in whom a cardiovascular disturbance was present and was unexplained on the basis of any factors ordinarily recognized as being of etiologic significance in circulatory failure. In all instances the history gave evidence of an unbalanced diet, and many patients showed other signs of deficiency states, such as "alcoholic" polyneuritis. As evidence of a direct relationship between cardiovascular symptoms and deficiency of vitamin B components, Weiss and Wilkins have used the following criteria: the history of an unbalanced diet, the beneficial response to foods rich in vitamin B or to concentrates or crystals of vitamin B₁, the simultaneous presence of other clinical manifestations recognized as deficiency states, such as polyneuritis, the absence of other recognizable etiologic factors of cardiac disease, the electrocardiographic changes which disappear after administration of vitamin B₁, and the similarity of the clinical syndrome and histologic picture of the heart muscle to those observed in beriberi in other parts of the world. It is clearly recognized that the evidence is presumptive and that proof has not been established. In studies of these patients the principal conclusions reached included the observations that dysfunction of the cardiovascular system might develop as a result of an unbalanced diet (especially one lacking in vitamin B) and that such dysfunction could affect both a previously normal and a previously damaged cardiovascular apparatus. The authors stated that they felt that these abnormalities depended partly on changes in the nervous system and partly on changes in the myocardium. The principal symptoms were simple tachycardia, vague

55 Wenckebach, K. F. *Das Beriberi-Herz. Morphologie, Klinik, Pathogenese, Pathologie und Klinik in Einzeldarst.* Berlin, Julius Springer, 1934, vol. 6.

56 Weiss, S., and Wilkins, R. W. *The Value of Cardiovascular Disturbances in Vitamin Deficiency States*, *Tr. A. Am. Physicians* **51** 341, 1936.

reflex irritability, with bradycardia or with asystole and syncope, and failure of the right or left side of the heart, peripheral arteriolar dilatation and vasomotor collapse, with vascular constriction, in various combinations. In one group of patients these changes disappeared rapidly, and in another they disappeared slowly after rest and an adequate dietary intake. Electrocardiographic changes were noted in all but 3 of 38 patients and consisted principally of changes in the T waves, in low amplitude and in prolongation of the electrical systole (Q-T), which usually disappeared under therapeutic measures. Histologic changes observed in the cardiac muscle in several patients were observed to be similar to those described by Wenckebach, but they were not considered characteristic or specific of deficiency states. Weiss and Wilkins expressed the opinion that the conditions they described were actually more frequent than has been noted previously. They wrote that such conditions should be looked for principally in examination of alcoholic addicts and less frequently in examination of pregnant women, of persons without work, of those living in conditions of poverty, of food cranks, of diabetic patients and of those with certain types of gastrointestinal disease. These groups of persons rarely perform hard work and this may be one of the factors which accounts for the great variability which has been noted in the degree of deficiency and in the variability of absence of symptomatic response.

It is extremely important not to ascribe to vitamin B deficiency cardiovascular symptoms or signs which cannot readily be explained on the basis of ordinary and well recognized conditions. Much more evidence will have to be presented before the field of cardiovascular changes in relation to vitamin B deficiency can be closely delineated. It is equally important to emphasize that the promiscuous use of preparations of vitamin B for relief of symptoms in all types of cardiovascular disease is useless and might prove dangerous. Weiss⁵⁷ pointed out that his studies of the effect of vitamin B₁ on the heart and circulation of normal subjects, in the presence of various types of organic heart disease and in the presence of different types of edema, revealed no changes in heart rate, in electrocardiographic tracings, in hemodynamics or in edema even though a dose as large as 30 or 40 mg of crystalline vitamin B₁ was given in a single injection.

Rabinowitz and Rogers⁵⁸ have reported an interesting case of a child 4 years of age who had a large heart, a rapid and irregular pulse, gallop rhythm, a precordial thrill and loud systolic and diastolic murmurs, with evidence also of scurvy and rickets. Four months after

⁵⁷ Weiss, Soma. Personal communication to the author.

⁵⁸ Rabinowitz, L., and Rogers, E. J. Reversion of Cardiac Enlargement in a Four Year Old Child Following Treatment for Avitaminosis, *New England J. Med.* **215** 621-623 (Oct 1) 1936.

dietary treatment the foregoing signs and symptoms had cleared, and the size of the heart was normal

The mechanism of formation of edema in relation to vitamin B₁ deficiency is still not clear. In some instances the edema is probably dependent, in part at least, on circulatory failure and in others on associated decrease in the plasma proteins, while in some cases, such as that of Elsom,⁵⁹ it remains unexplained. A relationship which might exist between vitamin B₁ and carbohydrate metabolism in diabetes and the possible therapeutic value of crystalline vitamin B₁ in the treatment of diabetes was mentioned in last year's review.⁶⁰ Acute and chronic disorders of the optic nerve and perhaps of the ocular muscles, hemorrhagic lesions of the retina and optic neuritis all have been ascribed to deficiency of vitamin B₁.

The occurrence of anorexia, achlorhydria, atrophy of the lingual papillae and hypotonicity and hypomotility of the gastro-intestinal tract all have been noted as evidence of vitamin B₁ deficiency. In an interesting study of the possible effect of vitamin B₁ deficiency on the gastric juice of man, Alvarez and his associates⁶¹ made daily observations on the gastric juice of 2 subjects over a period of six weeks while on a diet sufficiently deficient in vitamin B₁ to make the vitamin-calory ratio 1:2 (normal minimum, 1:8—Cowgill). No signs of vitamin B₁ deficiency developed, although the value for hemoglobin distinctly dropped and changes were not noted in the concentration of hydrochloric acid or pepsin in the gastric juice. In studies of experimental animals Simpson⁶² could not find atrophy, ulceration or erosion of the gastric mucosa of albino rats which were on a diet deficient in vitamin B₁, and he said he did not believe the slight changes he noted could be of any importance in the genesis of ulcer. These changes were moderate congestion and cellular infiltration. Kik, Sure and Buchanan⁶³ did not observe in the rat noteworthy changes in digestive efficiency of either the proteolytic or the amylolytic enzyme in the presence of deficiency of vitamin B or G. There was, however, a marked decrease in the

59 Elsom, K. O. Experimental Study of Clinical Vitamin B Deficiency, *J Clin Investigation* **14** 40-51 (Jan) 1935

60 Wilder, R. M., and Wilbur, D. L. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch Int Med* **57** 422-471 (Feb) 1936

61 Alvarez, W. C., Pilcher, F., Foley, Mary A., Mayer, Annette, and Osterberg, A. E. The Effects on the Gastric Juice of Man of Six Weeks' Deprivation of Vitamin B₁, *Am J Digest Dis & Nutrition* **3** 102-107 (April) 1936

62 Simpson, C. K. Observations upon Gastritis, *Guy's Hosp Rep* **86** 120-128 (Jan-April) 1936

63 Kik, M. C., Sure, B., and Buchanan, Kathryn S. Enzymic Efficiency in Avitaminosis. III. Influence of Vitamin B₁ and G Deficiencies on the Concentration of Blood and Tissue Enzymes, *Am J Digest Dis & Nutrition* **3** 490-492 (Sept) 1936

digestive efficiency of pancreatic esterase, and there was a marked decrease in the concentration of pancreatic and hepatic lipase in the presence of vitamin B deficiency, which suggests a disturbance in digestion of fats in this type of avitaminosis

Vitamin B₃—The importance of this factor in nutrition of man has not been established

Vitamin B₄—Little is known of the physiology of vitamin B₄. It may be related to certain adenine nucleotides or nucleosides. Elvehjem⁶⁴ has expressed the belief that this factor probably will find an important place in nutrition of man and in the treatment of certain disorders of the brain. It is not abundant in foods and is easily destroyed. Some workers believe that deficiency of vitamin B₄ is relieved by large doses of vitamin B₁ and therefore doubt the existence of vitamin B₄.

Vitamin B₅—The status of this factor is questionable

Vitamin B₆—This factor, which is one of the principal components of vitamin B₂, or G, is identical with the "factor Y" of Chick, Copping and Edgar⁶⁵ and with Gyorgy's⁶⁶ vitamin B₆. Its absence leads to the development of "rat pellagra." The factors of "rat pellagra," "chick pellagra" and "human pellagra" are apparently not identical, and consequently the relation of vitamin B₆ to pellagra of man remains to be defined.

Pellagra—The etiology of pellagra is still not entirely clear. Deficiency of vitamin B₂, or G, long has been associated with this disease, but a clearcut etiologic relationship has not been established. Vitamin B₂ (G) has been found to consist of at least two factors, one of which, lactoflavin, has been shown by Dann⁶⁷ to be of no therapeutic value in pellagra of man. The relation of the other factor, B₆, the chemical nature of which is uncertain, is not clear either. Elvehjem, for instance, stated that black tongue of dogs, which generally is accepted as identical with pellagra of man, is completely relieved by administration of a filtrate which remains after removal of flavins from vitamin B₂ (G). On the other hand, in their observations Birch, Gyorgy and Harris⁶⁸

64 Elvehjem, C. A. Present Status of the Vitamin B Complex, *Am J Pub Health* **25** 1334-1339 (Dec.) 1935

65 Chick, Harriette, Copping, Alice M., and Edgar, Constance E. The Water-Soluble B-Vitamins. IV The Components of Vitamin B₂, *Biochem J* **29** 722-734, 1935

66 Gyorgy, P. Investigations on Vitamin B₂ Complex. The Distribution of Lactoflavin and of "Pellagra-Preventing Factor" (Vitamin B₆) in Natural Products of Animal Origin, *Biochem J* **29** 760-766, 1935

67 Dann, W. J. The Vitamin G Complex in Rat Dermatitis and Human Pellagra, *J Biol Chem* **114** xxiv-xxv, 1936

68 Birch, T. W., Gyorgy, P., and Harris, L. J. I-VI The Vitamin B₂ Complex. Differentiation of the Antiblack-Tongue and the "P-P" Factors from Lactoflavin and Vitamin B₆ (So-Called "Rat Pellagra" Factor), *Biochem J* **29** 2830-2850, 1935

and Dann ⁶⁹ have been unable to relate vitamin B₆ to black tongue of dogs or to pellagra of man. Birch and his associates have reported the occurrence of pellagra of man when the diet was high in vitamin B₆.

Although, as has been noted, there is disagreement as to the nature of the significant dietary factors in pellagra, Sydenstriker and his collaborators ⁷⁰ suggested the existence of an "intrinsic" factor, which is deficient in pellagra. These workers offered the hypothesis that the intrinsic factor is present in gastric juice and that it makes possible utilization of minimal quantities of extrinsic factors. Variability in the capacity to retain or regenerate the intrinsic factor may explain some of the variabilities in therapeutic response of pellagrous patients.

The characteristic early cutaneous lesions of pellagra occur principally on exposed surfaces, and it has long been accepted that exposure to sunlight is a precipitating factor in this typical distribution. Spies ⁷¹ recently has studied this phase of the disease and has reported that pellagrous lesions occur in the absence of sunlight and may heal in the presence of exposure to sunlight or to ultraviolet radiation. Spies emphasized that pellagra should be considered a systemic disease and not a cutaneous condition and that under certain circumstances, still matters of conjecture, sunlight may act as an irritant and precipitate the cutaneous lesions of the disease.

Cardiac symptoms are rarely reported in pellagra, but Feil ⁷² reported abnormal electrocardiographic tracings for half of 38 patients with moderate to severe pellagra. In 14 of the 19 patients in whom changes were detected no other abnormalities which could influence the tracing were observed. The changes noted were inversion of the T wave in leads I or II or both, a Pardee type of S-T wave and a large T wave. Feil expressed the opinion that the heart is physiologically disturbed in this disease.

Of much practical clinical value is the report of Blankenhorn and Spies ⁷³ on the significance, recognition and treatment of oral complications of chronic alcoholism and of alcoholic pellagra. Approximately

69 Dann, W. J. The Vitamin G Complex. Non-Identity of Rat Dermatitis Due to Vitamin B₆ Deficiency and Dermatitis of Human Pellagra, *J. Nutrition* **11** 451-462 (May) 1936.

70 Sydenstriker, V. P., Armstrong, E. S., Derrick, C. J., and Kemp, P. S. On the Existence of Intrinsic Deficiency in Pellagra. Preliminary Report, *Am. J. M. Sc.* **192** 1-9 (July) 1936.

71 Spies, T. D. Relationship of Pellagrous Dermatitis to Sunlight, *Arch. Int. Med.* **56** 920-926 (Nov.) 1935.

72 Feil, H. Clinical Study of Electrocardiogram and of Phases of Cardiac Systole in Pellagra, *Am. Heart J.* **11** 173-184 (Feb.) 1936.

73 Blankenhorn, M. A., and Spies, T. D. Oral Complications of Chronic Alcoholism. Significance, Recognition and Treatment, *J. A. M. A.* **107** 641-642 (Aug. 29) 1936.

60 per cent of 200 alcoholic addicts were found to have on the mouth and tongue specific lesions of widespread stomatitis. The tongue becomes swollen so that impression of the teeth can be seen on its surface, it becomes bright red and ulceration may occur. The gums and mucous membrane may share in this process. Early treatment, consisting of a nutritious diet of 4,000 calories and 75 Gm of yeast or of liver extract daily, caused the lesions to disappear.

Methods of Recognition and the Frequency of States of Deficiency from Lack of the Components of the Vitamin B₁ Complex—Knowledge of these matters remains in the process of evolution. According to Youmans, no reliable symptoms, signs or diagnostic tests are available for detection of conditions of minimal vitamin B₁ deficiency. However, a variety of clinical symptoms exist which should lead one to suspect the possibility of such deficiency. The occurrence of neuritis of the peripheral or optic nerves, of circulatory changes previously noted, of unexplained edema and of vague but suggestive digestive symptoms, such as anorexia, achlorhydria and poor intestinal tonicity, particularly if patients have been on an inadequate diet, should lead perhaps to a suspicion of deficiency. Estimation, with Cowgill's formula, of the vitamin B₁ requirement of the subject and of his previous intake might be helpful as additional evidence. As yet estimations of the vitamin B₁ content of the blood and urine require extensive laboratory and biologic facilities and are therefore not practicable for ordinary use, also the lower limit of vitamin adequacy has not been clearly established for man. Therapeutic tests with crystalline vitamin B₁ also are of diagnostic value, but favorable response to injections of this substance is not proof that the patient suffered from a deficiency of the vitamin.

The diagnosis of pellagra still depends on clinical judgment. Glossitis, diarrhea, digestive disturbances and nervous and mental disorders are no more than suggestive. The cutaneous symptoms may be characteristic. Response of such symptoms to administration of yeast and other preparations rich in the vitamin B complex may constitute further evidence.

The frequency of lesions resulting from vitamin B deficiency is uncertain. The observations of Weiss and Wilkins, of Youmans and of Scott and Herrmann⁷⁴ suggest that states of vitamin B₁ deficiency may be more common than has previously been thought, but more objective evidence is necessary before certain knowledge of the frequency of the disorder can be obtained. Attention should be directed to the occurrence of so-called secondary pellagra in the northern part of the United States, namely, pellagra secondary to or associated with organic disease of the digestive tract, particularly obstructing and malignant diseases.

⁷⁴ Scott, L. C., and Herrmann, G. R. Beriberi ("Maladie des Jambes") in Louisiana, with Especial Reference to Cardiac Manifestations, J. A. M. A. 90: 2083-2090 (June 30) 1928.

VITAMIN C

In an excellent review of the chemistry and physiologic activity of vitamin C, King⁷⁵ pointed out that the period since 1932 has witnessed the identification and establishment of the molecular structure of vitamin C, as well as many exact measurements of its physiochemical properties, its synthesis, its commercial production and the development of many methods of analysis and of detailed knowledge of its occurrence in plant and animal tissues. Moreover, a certain degree of correlation with specific enzyme systems has been worked out and steady but slow advance has been made in understanding its significance in relation to the health of man. As far as animal tissues are concerned, the two specific rôles for vitamin C which seem to have been clearly established are in respiratory function and in regulation of the colloidal condition of the intercellular substance. Its rôle in relation to respiratory function has to do with the vitamin serving as an agent for transporting hydrogen between unidentified metabolites and other carriers or molecular oxygen, by way of two or more oxidase enzyme systems. It appears likely that the vitamin affects directly or indirectly many additional types of chemical change. Clinical interest has been centered principally around the rôle of vitamin C in the regulation of the colloidal condition of the intercellular substance, because the hemorrhagic tendency which is so characteristic of scorbutic states is the result principally of alterations in the intercellular substance of capillary walls.

Vitamin C is water soluble and readily diffusible and therefore is usually easily absorbed from the gastro-intestinal tract. According to Klodt,⁷⁶ this absorption occurs principally in the upper part of the intestine. He expressed the belief that bile may aid in the absorption, since it retards oxidation of vitamin C in dilute solutions. Under normal circumstances variable amounts of the vitamin are lost in the stool or destroyed in the gastro-intestinal tract. Measurements of the vitamin C content of a large variety of tissues, as well as that of the blood and urine, have been made, in fact, the vitamin C content of a single cell can be estimated with a fair degree of accuracy. The vitamin C content is highest in glandular tissues and lowest in muscle and stored fat. Glick and Biskind,⁷⁷ using a microchemical method sensitive to ± 0.0001 mg of vitamin C, have examined the content of this vitamin in the various tissues of cattle. The highest recorded value is in the pars intermedia of the pituitary body, which contains one and one-half

75 King, C. G. Vitamin C, Ascorbic Acid, *Physiol Rev* **16** 238-262 (April) 1936.

76 Klodt, W. Influence of Bile on Resorption of Vitamin C, abstr, *J A M A* **106** 2036 (June 6) 1936.

77 Glick, D., and Biskind, G. R., cited in Distribution of Cevitamic Acid in Tissues, editorial, *J A M A* **107** 1135-1136 (Oct 3) 1936.

times more than the pars distalis of the pituitary body or the adrenal cortex. The amount present in the corpus luteum roughly parallels the amount of luteal hormone, progesterone, in the ovary.

Methods of testing the vitamin C content of urine depend on the capacity of the vitamin as a reducing substance. The principle involved rests on the reduction of the vitamin in the urine by titration with the dye 2,6-dichlorophenol-indophenol. The principal sources of error include the presence of other reducing substances in urine and the destruction of vitamin C in urine which is allowed to stand without adequate preservative measures. Sendroy and Schultz⁷⁸ have shown that the important factors in the preservation of cevitamic acid in the urine are oxygen tension, temperature and p_H , particularly the first. Urine to be tested should be titrated immediately after it has been voided, or it may be preserved by addition of 10 per cent by volume of glacial acetic acid or it may be kept in a refrigerator in a small container from which air is excluded. Sendroy and Schultz estimated that their titrations approximated within 10 to 15 per cent of the total cevitamic acid content of the urine. A ferricyanide method of titration of urine for vitamin C has been used by Tauber and Kleiner⁷⁹.

The quantity of vitamin C in the twenty-four hour output of urine of normal subjects is variable and depends principally on two factors: the first is the relative approach to saturation of the tissues of the subject, and the second is the intake of vitamin C during the period over which tests are made. Harris and Ray⁸⁰ placed the average in the twenty-four hour output of urine of normal subjects at from 30 to 33 mg. Johnson and Zilva⁸¹ stated as their conclusion that there is no definite standard of normality as regards urinary excretion, while Wright⁸² has found the average normal excretion to be from 20 to 30 mg. daily. However, Youmans and his colleagues⁸³ reported that

78 Sendroy, J., Jr., and Schultz, M. P. Studies of Ascorbic Acid and Rheumatic Fever. Quantitative Index of Ascorbic Acid Utilization in Human Beings and Its Application to Study of Rheumatic Fever, *J. Clin. Investigation* **15** 369-383 (July) 1936.

79 Tauber, H., and Kleiner, I. S. A Method for the Quantitative Determination of Ascorbic Acid (Vitamin C). The Vitamin C Content of Various Plant and Animal Tissues, *J. Biol. Chem.* **108** 563-570, 1935.

80 Harris, L. J., and Ray, S. N. Diagnosis of Vitamin-C Subnutrition by Urine Analysis, with Notes on Antiscorbutic Value of Human Milk, *Lancet* **1** 71-77 (Jan. 12) 1935.

81 Johnson, S. W., and Zilva, S. S. The Urinary Excretion of Ascorbic and Dehydro-Ascorbic Acids in Man, *Biochem. J.* **28** 1393-1408, 1934.

82 Wright, I. S. The Present Status of the Clinical Use of Ceovitamic Acid (Ascorbic Acid) (Crystalline Vitamin C), *Am. J. M. Sc.* **192** 719-735 (Nov.) 1936.

83 Youmans, J. B., Corlette, M. B., Akeroyd, J. H., and Frank, H. Studies of Vitamin C Excretion and Saturation, *Am. J. M. Sc.* **191** 319-333 (March) 1936.

half of 16 normal controls whose diets were supposedly adequate excreted less than 20 mg daily. These results suggest the variability which probably exists in normal subjects and emphasizes the fact that few, if any, conclusions can be drawn from isolated determinations of the urinary output of vitamin C.

Methods of determination of the reduced cevitamic acid content of the blood serum and plasma have been developed by Abt, Farmer and Epstein⁸⁴ and by Taylor, Chase and Faulkner⁸⁵.

Taylor and his associates reported that in studies of 33 subjects who were free from infection or scurvy the average level of reduced cevitamic acid in the blood plasma was found to be 1.61 mg per hundred cubic centimeters, with extreme values of 0.83 and 2.43 mg. Abt and his associates stated as their conclusion that values of less than 0.75 or 0.8 mg of reduced cevitamic acid per hundred cubic centimeters of blood plasma indicate a subnormal intake of vitamin C. Wright, using the method of Abt, Farmer and Epstein, found the normal level in adults to rest between 0.7 and 1.3 mg per hundred cubic centimeters of blood.

The classic clinical picture of scurvy is infrequently seen, but reports of subclinical and preclinical scurvy, diagnosis of which has been based principally on studies of capillary fragility or on the results of urinary excretion of a variety of test doses of vitamin C, have appeared frequently in the literature. It seems obvious that there is a wide zone of vitamin deficiency between scurvy and optimal health. How satisfactorily quantitative tests of the intake and output of vitamin C and of its concentration in the blood plasma of patients can be used to determine the position of a patient in this zone is uncertain. However, it must be emphasized that until more is known about the actual daily requirement of vitamin C, about the significance of saturation and about the clinical value of test doses, caution must be used in the interpretation of many conditions now called "subclinical" scurvy.

Studies of "capillary fragility," or "capillary resistance," have been used for several years as a measure of the adequacy or inadequacy of vitamin C nutrition. A variety of different methods of performing the test have been developed, and this has further tended to confuse the issue. Wright has well summarized the situation in pointing to the three distinct schools of thought in regard to the diagnostic significance of the method.¹ Those of one school believe that the phenomenon is useful and important and that a positive pressure method is probably

⁸⁴ Abt, A. F., Farmer, C. J., and Epstein, I. M. Normal Cevitamic (Ascorbic) Acid Determinations in Blood Plasma and Their Relationship to Capillary Resistance, *J. Pediat.* **8** 1-19 (Jan.) 1936.

⁸⁵ Taylor, F. H. L., Chase, D., and Faulkner, J. M. The Estimation of Reduced Ascorbic Acid in Blood Serum and Plasma, *Biochem. J.* **30** 1119-1125 (July) 1936.

the most satisfactory one 2 Those of another school believe that the phenomenon is useful and important, but they feel that a negative pressure method is more reliable and acceptable 3 Those of still another school feel that studies of the vitamin content of the urine and blood reveal the entire picture and that the capillary fragility tests are misleading and of little value

Any one who takes the time to review the literature in regard to this interesting and important phase of nutrition cannot fail to be impressed by the variability of the results which have been reported There can be no question that increased capillary fragility is non-specific and occurs in a variety of conditions other than deficiency of vitamin C, such as thrombocytopenic purpura and increased capillary fragility resulting from the toxic effects of nearsphenamine, carbon monoxide, scarlet fever and diphtheria, as well as anemia Failure of patients with scurvy to give evidence of increased capillary fragility has been noted by Weld⁸⁶ On the other hand, there is not always a clear-cut correlation between the levels of cevitamic acid in the plasma and the urine and the results of capillary fragility tests (Abt, Farmer and Epstein and Wright) It seems obvious, therefore, that final conclusions cannot be made as yet delineating the diagnostic value of the various methods It is logical that a positive result of the capillary fragility test should lead to the suspicion of a state of deficiency of vitamin C and that much weight would be added to this suspicion if the test became negative after administration of cevitamic acid However, if scurvy and prescorbutic states are attributable solely to deficiency of vitamin C, then final proof of the presence of such a condition will have to depend on the demonstration, by objective quantitative data, of a deficiency in levels in the plasma and urine or in the response to a test dose of vitamin C As yet these values have not been satisfactorily defined for normal subjects

The administration of test doses of vitamin C to determine the "saturation," "retention," "reserve" and "resaturation" of vitamin C has been reported to be of value in determining the nutritive status of a subject with respect to vitamin C or as a diagnostic test of a prescorbutic state Some of these tests should prove to be of great value when normal standards have been established It does not seem reasonable to suggest that a subject must be saturated with vitamin C in order to avoid being classed as one suspected of having prescorbutic or preclinical scurvy There is considerable difference of opinion in regard to the value of such test doses Youmans and his colleagues reported that, in general, tests of saturation correspond to the tests of daily excretion and the probable dietary intake of the vitamin and

⁸⁶ Weld, C B Capillary Resistance Test and Its Relation to Vitamin C and D, *J Pediat* 9 226-233 (Aug) 1936

that a daily excretion of 20 mg and an excretion of 30 per cent of a test dose (about 600 mg in adults) are suggested as the lower limits of normal daily excretion and of saturation, respectively Sendroy and Schultz, on the other hand, suggested that the urinary excretion test of cevitamic acid is largely affected by the two variable factors relative approach to saturation of the tissues at the beginning of the test and the intake in the diet of the subject during the course of the test. If one can maintain this second factor constant by bringing about ingestion and absorption of fixed high doses of cevitamic acid, the results of the test may be taken as a measure of the first factor namely, the approach to saturation. The investigators named therefore proposed that the total of seven days' excretion under conditions of high daily test dose of 250 mg of cevitamic acid would be informative. Under such circumstances these workers have prepared a table of the "utilization coefficient" of vitamin C at various ages. In studies of the saturation and reserve of vitamin C, O'Hara and Hauck⁸⁷ reported that the amount of vitamin C necessary to restore the tissues to saturation after a month on a diet low in vitamin C ranged from 2,200 to 2,800 mg when administered in daily doses of 200 mg. They estimated the tissue reserves at saturation to be about 2,500 to 3,000 mg. In their observations of the excretion of cevitamic acid Archer and Graham⁸⁸ found evidence that the percentage output is much more valuable evidence that a patient has scurvy than is the amount of cevitamic acid taken before the excretion increased or the amount excreted after a test dose. They suggested that one should measure the amount of cevitamic acid which must be given before the percentage output rises above 75 per cent.

The development of deficiency states does not always indicate a previously inadequate diet. Abnormalities of absorption and abnormal metabolic demands may precipitate such conditions in the face of an adequate diet. As Gagyi⁸⁹ has pointed out, there are two types of avitaminosis C. One is an alimentary type, and the other is a toxic type, usually observed in the course of infectious diseases. An excellent example of the alimentary type of scurvy is the case reported by Moncrieff⁹⁰ in which scurvy developed in an infant while it was on an adequate diet, the scurvy was promptly relieved by intravenous

87 O'Hara, Patricia H., and Hauck, Hazel M. Storage of Vitamin C by Normal Adults Following a Period of Low Intake, *J Nutrition* **12** 427-413 (Oct 10) 1936

88 Archer, H. E., and Graham, G. Some Observations on the Excretion of Ascorbic Acid, *Lancet* **1** 710-713 (March 28) 1936

89 Gagyi, J. Ueber die bactericide und antitoxische Wirkung des Vitamin C, *Klin Wchnschr* **15** 190-195 (Feb 8) 1936

90 Moncrieff, A., quoted in Unexpected Rickets and Scurvy, annotation, *Lancet* **1** 36 (Jan 4) 1936

administration of vitamin C. The inhibitory effect which the vitamin has on diphtheria toxin, and probably also on other products of pathogenic organisms, may be one of the normal defense mechanisms of man. It probably explains, in part at least, the frequently observed low values for cevitamic acid in the blood and urine in the presence of infections. The prophylactic and therapeutic use of vitamin C in infections has not produced clearcut results. Encouraging reports have been made of its use in association with hormones of the adrenal cortex in the presence of diphtheria, although it does not supplant diphtheria antitoxin. Encouraging studies of Jungeblut⁹¹ have suggested that it may be of value in inactivation of poliomyelitis virus in the experimental animal. Wright has reported that as a prophylactic against acute infections, such as tonsillitis, otitis media and abscess, large doses of vitamin C were not of value. Heise and Martin⁹² expressed the belief that in pulmonary tuberculosis there is a rough parallelism between the activity of the disease and the daily excretion of vitamin C in the urine when the patient is on a controlled diet. They estimated that the patient who has tuberculosis requires from 55 to 138 mg. of cevitamic acid to maintain a normal rate of excretion, as compared with the normal requirement of from 15 to 30 mg. Hasselbach⁹³ placed the daily requirement, in the presence of active pulmonary tuberculosis, at the equivalent of from 100 to 150 mg. of orange juice.

The relation of gastro-intestinal abnormalities to absorption of vitamin C is indicated by the studies of Einhauser,⁹⁴ who reported that when patients have what he called "gastro-intestinal catarrh," there is disturbance in absorption of vitamin C. This is particularly true if patients have achlorhydria, then more rapid oxidative decomposition of vitamin C is said to result from the increased alkalinity of the intestinal content, as well as from the pathologic bacterial flora, which destroys vitamin C. Whether vitamin C is a significant factor in the etiology of gastric and duodenal ulcer, or perhaps in hemorrhages which occur from such lesions, is an important practical point. Schultzer's⁹⁵ studies indicated that the capillary resistance in such cases is not abnor-

91 Jungeblut, C. W. Inactivation of Poliomyelitis Virus in Vitro by Crystalline Vitamin C (Ascorbic Acid), *J. Exper. Med.* **62** 517-521 (Oct.) 1935.

92 Heise, F. H., and Martin, G. J. Ascorbic Acid Metabolism in Tuberculosis, *Proc. Soc. Exper. Biol. & Med.* **34** 642-644 (June) 1936.

93 Hasselbach, F. Vitamin C und Lungentuberkulose, *Ztschr. f. Tuberk.* **75** 336-347 (July) 1936.

94 Einhauser, M. C-Vitamin und Gastroenteritis, *Ztschr. f. d. ges. exper. Med.* **98** 461-477, 1936, abstr., *J. A. M. A.* **107** 548 (Aug. 15) 1936.

95 Schultzer, Paul. Studies on Capillary Resistance. III. Improbability of C-Avitaminosis as Etiological Factor in Peptic Ulcer, *Acta med. Scandinav.* **83** 555-564, 1934.

mal as compared with the normal. However, Archer and Graham⁹⁶ reported that in 9 patients with ulcer they found less saturation with vitamin C than in 2 control subjects who gave rather low values for the vitamin. Similarly, Harris, Abbasy, Yudkin and Kelly⁹⁷ found in patients with ulcer in a large hospital an average urinary excretion of 5.6 mg of vitamin C in twenty-four hours, while the average for 74 adult patients in the hospital was 8.9 mg. It seems clear that in most of these cases the low values were related to a low intake of vitamin C on ordinary therapeutic diets for ulcer. It is questionable if lack of vitamin C is more than a secondary factor in causation of ulcer under such circumstances. Its relation to hemorrhage from ulcer is still unsettled and obviously requires close scrutiny.

Interesting but conflicting reports of the relation of vitamin C to pigmentation of the skin have appeared recently. Szent-Gyorgyi,⁹⁸ in 1934, reported decrease in the pigmentation in Addison's disease following the use of cevitic acid. Wilkinson and Ashford⁹⁹ studied 3 patients with Addison's disease and found in all of them deficiency in vitamin C, they did not obtain distinct change in pigmentation at first but definitely less pigmentation after vitamin C had been administered for some time. In a case of pernicious anemia, with pigmentation of the face, Schroeder and Einhauser¹⁰⁰ did not observe change in the pigmentation following the use of liver extract but prompt lessening of the pigmentation when 300 mg of synthetic vitamin C was given intravenously for fourteen days.

Further attempts to relate rheumatic fever and chronic infectious arthritis to deficiency of vitamin C have been made by Rinehart,¹⁰¹ on the basis of the similarity of lesions observed in man in these conditions and those observed in scorbutic animals with added infection. The studies of Sendroy and Schultz and of Schultz¹⁰² failed to support the concept that a condition of deficiency of cevitic acid is a predis-

96 Archer, H. E., and Graham, G. The Subcurvy State in Relation to Gastric and Duodenal Ulcer, *Lancet* **2** 364-366 (Aug 15) 1936.

97 Harris, L. J., Abbasy, M. A., Yudkin, J., and Kelly, S. Vitamins in Human Nutrition. Vitamin-C Reserves of Subjects of the Voluntary Hospital Class, *Lancet* **1** 1488-1490 (June 27) 1936.

98 Szent-Gyorgyi, A., quoted by Wright and Lilienfeld¹⁰³

99 Wilkinson, J., and Ashford, C. A. Vitamin C Deficiency in Addison's Disease, *Lancet* **2** 967 (Oct 24) 1936.

100 Schroeder, H., and Einhauser, M. Ueber einen Zusammenhang zwischen gestörter Vitamin-C-Resorption und pathologischer Pigmentierung bei Gastroenteritis und Achylia gastrica, *Munchen med Wchnschr* **83** 923-925 (June 5) 1936.

101 Rinehart, J. F. An Outline of Studies Relating to Vitamin C Deficiency in Rheumatic Fever, *J. Lab & Clin Med* **21** 597-604 (March) 1936.

102 Schultz, M. P. Studies of Ascorbic Acid and Rheumatic Fever. Test of Prophylactic and Therapeutic Action of Ascorbic Acid, *J. Clin Investigation* **15** 385-391 (July) 1936.

posing factor in the causation of rheumatic fever, these studies revealed also that clinical manifestations of this disease were not demonstrably affected by the oral or intravenous administration of vitamin C over periods of several months. Certainly further observations should be carried out in this interesting field.

In view of the hemorrhagic tendency in scurvy, it was obvious that attempts would be made to relate all types of hemorrhagic diseases to vitamin C deficiency and to treat them with the vitamin. Disappointment has followed almost all such attempts, particularly in thrombocytopenic purpura, leukemia, Schonlein's purpura and hemophilia. Treatment of hemorrhagic states with vitamin C should not be carried out blindly but should depend on as clearcut evidence as possible that a deficiency of cevitamic acid exists.

Recognition, Frequency and Treatment of States of Vitamin C Deficiency—The recognition of scurvy is not difficult, but determination of the presence of states of subclinical scurvy or hypovitaminosis C may be extremely difficult. Clinical features which might possibly lead to the suspicion that the disease is present include hemorrhagic tendencies, dental caries, spongy gums, abnormal cutaneous pigmentation, vague aches and pains, as well as fatigue, pallor, frequent infections, anemia and a history of an inadequate diet.

If suspicions are aroused, the next step to take in determining the presence of vitamin C deficiency is to perform the capillary resistance test (for technic, see Wright and Lilienfeld¹⁰³). If the test shows a positive result, the evidence is suggestive but not conclusive. A negative test does not definitely exclude vitamin C deficiency. After this a therapeutic test, performed by administration of vitamin C orally or intravenously, with relief of symptoms or reversal of previously positive results of the capillary test, probably would be good evidence that the deficiency exists. Studies of the level of cevitamic acid in the blood and urine and the results of test doses give more objective evidence of the status of vitamin C nutrition (see foregoing section for details). However, normal values have not as yet been conclusively established.

The frequency of states of preclinical scurvy, or vitamin C hypovitaminosis, is unknown, but they are probably more common than previously was believed, particularly among members of the lower economic groups, among patients who have chronic infectious diseases and among those who are under prolonged and restricted dietary care. How frequently these states will be found among the general population will depend on observations in the future, based on standards as yet incompletely established.

103 Wright, I. S., and Lilienfeld, A. Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid), with Especial Reference to Its Effects on Capillary Fragility, *Arch. Int. Med.* **57** 241-274 (Feb.) 1936.

The normal daily requirement of cevitic acid of an adult is probably between 20 and 50 mg. Ordinary therapeutic doses are usually 200 mg. or less and may be given orally or intravenously. It is advocated by some to give to patients suspected of vitamin C deficiency 1,000 mg. daily for several days and thereafter to administer maintenance doses (30 to 50 mg.) with the idea of approaching saturation and of overcoming any tendency to deficiency which may exist.

VITAMIN D

Interest in vitamin D has been much increased because of the apparent multiplicity of substances which possess antirachitic properties. Because of variabilities in absorption and utilization of these substances by the same and different species of experimental animals, the difficulty of the problem has been multiplied. Further difficulties have arisen because of the variability in reports arising from the multiplicity of products formed by the irradiation of ergosterol. Bills¹⁰⁴ has presented evidence from chemical studies and bio-assays that at least eight distinct forms of the vitamin have been prepared by irradiation of materials containing provitamins. The three common sources of animal origin—fish liver oils, viosterol and irradiated milk—represent at least three chemically different vitamins D. From an extensive review of the literature Jeans¹⁰⁵ gave as his conclusion that vitamin D of animal source appears to be more potent for the use of man than vitamin D of vegetable source. Those interested in the chemical problems of vitamin D are referred to the excellent summaries of Bills¹⁰⁴ and McCollum¹⁰⁶.

The mode of action of vitamin D is little understood. It is essential for adequate mineralization of bones and teeth and is therefore closely related to the metabolism of calcium, phosphorus and parathyroid hormone. Heymann¹⁰⁷ recently scrutinized this problem, particularly from the standpoint that vitamin D may act in a hormonal rôle in phosphate metabolism, as parathyroid hormone acts in calcium metabolism. He could find no evidence for such a hypothesis, although he found that vitamin D increased the diminished inorganic phosphate content of the

104 Bills, C. E. New Forms and Sources of Vitamin D, *J. A. M. A.* **108** 13-15 (Jan. 2) 1937.

105 Jeans, P. C. Vitamin D Milk. The Relative Value of Different Varieties of Vitamin D Milk for Infants, a Critical Interpretative Review, *J. A. M. A.* **106** 2066-2069 (June 13), 2150-2159 (June 20) 1936.

106 McCollum, E. V. The Fat-Soluble Vitamins, in Luck, J. M. Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1936, vol. 5, pp. 379-402.

107 Heymann, W. Studies on the Mode of Action and the Metabolism of Vitamin D, *J. Pediat.* **8** 480-488 (April) 1936.

blood in rickets Nicolaysen,¹⁰⁸ in his study of the mode of action of vitamin D in rats, suggested that its action in phosphate metabolism is to increase the supply of phosphate from the intestinal contents to the blood stream and thence to the tissues. He could not produce evidence that it acted by maintaining a balance between the different forms of phosphorus in the organism. Warkany¹⁰⁹ recently has reported attempts at estimation of the vitamin D content of the blood serum. Using a method of bio-assay, he found that in man the values are from 45.9 to 135 U. S. P. units for each hundred cubic centimeters of serum, with an average value of 99.09 units. When rabbits were given by mouth 0.1 cc of viosterol containing 100,000 U. S. P. units, there was elevation of the level of vitamin D in the serum in six hours. In twenty-four hours the maximal rise was present, amounting to about 2,700 U. S. P. units for one hundred cubic centimeters. This level was maintained for three or four days, it gradually became decreased, and normal levels were not attained until from four to six weeks later. During this period significant changes in phosphorus, calcium or phosphatase content of the serum were not noted.

There has been much controversy in recent years over the effectiveness of various therapeutic measures in the prevention of rickets and the healing of the lesions. Friedman,¹¹⁰ in 1934, after an extensive review of the literature, pointed out, for example, that there is extensive clinical evidence to the effect that far fewer units of vitamin D in the form of milk containing vitamin D are required to protect against rickets or to heal rachitic lesions than are required with other anti-rachitic agents. This subject has been reviewed again this year (1936), for the Council on Foods of the American Medical Association, by Jeans, and with material made available from reports in recent years, he concluded that "such evidence as is available may be interpreted to show that cod liver oil, cod liver oil concentrate milk, and irradiated milk are of equal potency for the human being, unit for unit."

One source of error which may be overlooked by clinicians is the translation of results of work on the prevention of rickets and healing of rachitic lesions in rats and chickens to results obtainable in rickets of infants. No clearcut relation has been established among these groups. Massengale and Bills¹¹¹ explained that the conflicting reports

108 Nicolaysen, R. Studies upon the Mode of Action of Vitamin D. I. Investigations upon the Phosphorus Compounds in Muscles, Liver and Kidneys as Influenced by Different Levels of Vitamin D and Phosphorus in the Diet, *Biochem J* **30** 1329-1337 (Aug.) 1936.

109 Warkany, Josef. Estimation of Vitamin D in Blood Serum, *Am J Dis Child* **52** 831-847 (Oct.) 1936.

110 Friedman, S. Vitamin D Milk—a Résumé, *J Pediat* **4** 678-692 (May) 1934.

111 Massengale, O. N., and Bills, C. E. A Quantitative Method for the Assay of Vitamin D with Chickens, *J Nutrition* **12** 429-446 (Nov.) 1936.

on the relative effectiveness, rat unit for rat unit, of cod liver oil and viosterol for chicks lies in the fact that these materials are not broadly comparable. Their relative efficacy fluctuates with the degree of calcification. The difference is small at low calcification, one hundred times at "normal" calcification and great in production of extra hard bone.

Another source of error may be the frequency of administration and the dilution of the preparation that contains vitamin D, since absorption is undoubtedly an important factor. Lewis¹¹² has observed, for example, that in a group of 441 infants given vitamin D at three different levels (145, 290 and 1,450 units of crystalline vitamin D) in 28 ounces (840 cc) of milk, in 7 drops of corn oil or in 7 drops of propylene glycol, rickets developed in those who received milk less frequently than in the others.

While the conclusion based on the work of many observers seems acceptable that, unit for unit, animal sources of vitamin D are essentially equal in antirachitic potency, there has been divergence of opinion in regard to the relative effectiveness of "yeast milk" (milk from cows fed irradiated yeast).

Evidence has been presented by Haman and Steenbock¹¹³ that in the chick a distinct difference exists between the antirachitic activity of "yeast milk" and "irradiated milk." In fact, yeast milk was approximately a tenth as effective as irradiated milk. Bethke and his co-workers¹¹⁴ obtained similar results. In a clinical study Davidson and his associates¹¹⁵ reported that the feeding of yeast milk to premature infants as the sole source of vitamin D proved to be inadequate for achieving complete protection against rickets. As a result of his review, Jeans has concluded that, on the basis of unit for unit, yeast milk and viosterol milk are of the same value, that irradiated milk and cod liver oil concentrate milk are of the same value and that irradiated milk is superior to yeast milk, but on the basis of a difference probably not more than 15:1. This ratio is based entirely on curative experiments, and, as Jeans pointed out, corroboration by preventive experiments is highly desirable.

112 Lewis, J. M. Further Observations on the Comparative Antirachitic Value of Crystalline Vitamin D Administered in Milk, Corn, Oil, or in Propylene Glycol, *J. Pediat.* **8** 308-314 (March) 1936.

113 Haman, R. W., and Steenbock, H. The Differential Antirachitic Activity of Vitamin D Milks, *J. Nutrition* **10** 653-666 (Dec.) 1935.

114 Bethke, R. M., Krauss, W. E., Record, P. R., and Wilder, O. H. M. The Comparative Antirachitic Efficiency of Vitamin D in Irradiated Milk, Metabolized (Yeast) Milk, and Cod Liver Oil, *J. Nutrition* **11** 21-30 (Jan) 1936.

115 Davidson, L. T., Merritt, K. K., and Chipman, S. S. Prophylaxis of Rickets in Premature Infants with Vitamin D Milk, *Am. J. Dis. Child* **51** 1-16 (Jan) 1936.

The constituent of milk which is important in increasing its anti-rachitic potency has been shown by Supplee and his associates¹¹⁶ to be associated with the lactalbumin fraction

Of greatest practical value in the problem of vitamin D is the dosage of the vitamin in the prophylaxis and treatment of rickets. In an excellent summary of their experience with viosterol over a period of six years at the Johns Hopkins Hospital, Shelling and Hopper¹¹⁷ stated the conclusion that for full term infants a daily dose of 5 drops of viosterol, containing about 1,125 U S P units, is efficacious in preventing rickets. For prematurely born infants and for babies growing at a too rapid rate, it may be advisable to administer from 15 to 20 drops of viosterol daily for the first three or four months of life and thereafter 5 drops, as for full term infants. In the treatment of rickets these workers employed doses of from 15 to 60 drops of viosterol daily, depending to some extent on the severity of the disease and the age of the infant or child. The average period required for healing was three and seven-tenths months. In groups receiving from 30 to 60 drops daily the average time for healing was not shortened, indicating that larger amounts than 20 drops of viosterol daily are not always more efficacious in inducing more rapid healing. Total refractoriness to viosterol was not encountered in the entire series, and partial refractoriness was noted in 1 case only. Toxic manifestations were never encountered, in spite of the fact that some children received viosterol in doses of from 30 to 60 drops daily for many months. Jeans concluded that animal-source vitamin D milk, with 135 U S P units to the quart (1,000 cc), will prevent rickets but that prevention of rickets is not a criterion of the adequacy of intake of vitamin D. He expressed the belief that animal-source vitamin D in the amount present in 1 standard teaspoonful of average high grade cod liver oil or in milk containing 400 U S P units to the quart (1,000 cc) is adequate for the infant from the standpoint of retention of calcium and growth. Beyond the age of infancy the exact requirement of vitamin D under any specified condition is unknown, but it appears to be increased during pregnancy and lactation.

The relation of diet, and particularly of vitamin D to dental caries was emphasized in last year's review. Since that time a final report¹¹⁸

116 Supplee, G. C., Ansbacher, S., Bender, R. C., and Flanagan, G. E. The Influence of Milk Constituents on the Effectiveness of Vitamin D, *J. Biol. Chem.* **114** 95-107 (May) 1936.

117 Shelling, D. H., and Hopper, Katherine B. Calcium and Phosphorous Studies. XII Six Years' Clinical Experience with Viosterol in the Prevention and Treatment of Rickets, Tetany, and Allied Diseases, *Bull. Johns Hopkins Hosp.* **58** 137-211 (March) 1936.

118 The Relation of Diet to Dental Caries, editorial, *Lancet* **2** 280-282 (Aug 1) 1936. Diet and the Teeth, editorial, *ibid.* **2** 287-288 (Aug 8) 1936.

of the Committee on Dental Disease, appointed by the Medical Research Council, in England, has been issued, entitled "Influence of Diet on Caries in Children's Teeth" Among the conclusions is the following statement

The investigations described in this report show conclusively that a relatively high vitamin D content of the food can do much to diminish the incidence of caries if the vitamin is given during the development of the teeth, that a beneficial effect may be obtained if the vitamin is given at a fairly late stage of development, and that even when it is given after the eruption of the teeth, the onset and spread of caries is delayed

Concerning the series of 290 children carefully studied for a period of two and a half years, the committee reported that the addition of cod liver oil or vitamin D to the basal diet (which was a good one) reduced by half the incidence of caries in newly erupted teeth To some extent a prophylactic effect was noted on previously erupted permanent and deciduous teeth

The use of vitamin D to aid the healing of fractures has led to a variety of opinions, and conclusions will not be possible until further controlled work has been done Deficiency of vitamins A and D or of vitamin D alone in the presence of experimental fractures in guinea-pigs leads to defective healing, principally because of defective formation of cartilage in the callus, according to Hertz,¹¹⁹ who has provided an excellent summary of this problem

The rôle of vitamin D in the metabolism of calcium and the relation among calcium, phosphorus, parathyroid hormone and vitamin D have not been clearly elucidated In an interesting study of the etiology and diagnosis of hyperparathyroidism Wilder and Howell¹²⁰ stressed the important relation which has been shown to exist in experimental animals between insufficiency of vitamin D, on the one hand, and hyperplasia and hypertrophy of the parathyroid bodies, on the other hand It is possible that vitamin D may be of some significance in the development or activation of adenoma of the parathyroid glands or in hyperplasia of these glands in man

The use of large doses of vitamin D in cases of arthritis has been of considerable interest Dreyer and Reed,¹²¹ in a report of the progress in 280 unselected cases of arthritis, noted encouraging responses in many cases Relief of pain, lessened disability and improvement

119 Hertz, John, quoted in *Vitamins and the Healing of Fractures*, editorial, *Brit M J* **2** 980 (Nov 14) 1936

120 Wilder, R M, and Howell, L P *Etiology and Diagnosis in Hyperparathyroidism Review of One Hundred and Thirty-Five Proved Cases*, *J A M A* **106** 427-431 (Feb 8) 1936

121 Dreyer, I, and Reed, C I *The Treatment of Arthritis with Massive Doses of Vitamin D*, *Arch Phys Therapy* **16** 537-540 (Sept) 1935

in general condition were reported in relation both to infectious and to hypertrophic arthritis. On the other hand, the reports of Wyatt and his associates¹²² and of Vrtiak and Lang¹²³ revealed results about commensurate with those of other types of treatment for arthritis. Dreyer and Reed used doses of 200,000 U. S. P. units daily and maximal doses of 300,000 units. Care must be taken to avoid toxic doses. The usual symptoms of toxicity are anorexia and gastrointestinal and urinary irritability. Occasionally persons apparently may be sensitive to vitamin D, for Thatcher¹²⁴ reported the case of a child given large, but not excessive, doses of vitamin D, who died apparently of vitamin D hypervitaminosis and who presented calcification in the kidney of sufficient degree to be noted at postmortem examination.

Recognition of States of Vitamin D Deficiency—The diagnosis of well developed rickets is not difficult. In cases of mild involvement the most reliable method is roentgenologic examination of bones. Estimation of the phosphatase content of the serum also may be of value. For adults no definite criteria are available. Osteoporosis and changes in the levels of calcium and phosphorus in the serum may occur as a result of a variety of lesions involving calcium and phosphorus metabolism and the parathyroid bodies.

One might suspect vitamin D deficiency in patients with unusual or rapidly developing dental caries, osteoporosis, osteomalacia, tetany and insufficiently explained fractures. The condition is most likely to occur during pregnancy and lactation and in celiac disease, spile and chronic jaundice.

VITAMIN E

Interest in the possible clinical significance of vitamin E has arisen because of reports in the literature regarding the use of wheat germ oil in the treatment of habitual and spontaneous abortion. Evans and his associates¹²⁵ have announced the isolation and have described the properties of an alcohol, α -tocopherol, which has the properties of vitamin E. Of 11 patients subject to habitual abortion (three to fifteen abortions) Watson¹²⁶ reported that 9 went to term and were

122 Wyatt, B. L., Hicks, R. A., and Thompson, H. E. Massive Doses of Vitamin D in the Treatment of Proliferative Arthritis, *Ann Int Med* **10** 534-536 (Oct.) 1936.

123 Vrtiak, E. G., and Lang, R. S. Observations on the Treatment of Chronic Arthritis with Vitamin D, *J. A. M. A.* **106** 1828 (May 23) 1936.

124 Thatcher, L. Hypervitaminosis D, *Lancet* **1** 20-22 (Jan. 4) 1936.

125 Evans, H. M., Emerson, O. H., and Emerson, G. A. The Isolation from Wheat Germ Oil of Alcohol, α -Tocopherol, Having Properties of Vitamin E, *J. Biol. Chem.* **113** 319-332 (Feb.) 1936.

126 Watson, E. M. Clinical Experiences with Wheat Germ Oil (Vitamin E), *Canad. M. A. J.* **34** 134-140 (Feb.) 1936.

delivered of normal children and that 6 of them completed pregnancy for the first time Currie¹²⁷ also has reported good results Just what the relationship may have been between habitual abortion and vitamin E deficiency in these cases is uncertain The work of Rowlands and Singer¹²⁸ suggested that vitamin E helps to maintain the normal activity of the corpus luteum during early pregnancy, not by direct action but by stimulation of the gonadotropic functions of the pituitary body

The Cooperative Committee of the Council on Pharmacy and Chemistry and of the Council on Foods, previously mentioned, has declared that there is no evidence to indicate that vitamin E has any therapeutic merit and has suggested that the Council on Foods refuse to accept any vitamin E preparation

VITAMIN G (SEE VITAMIN B COMPLEX)

VITAMIN K

Considerable interest has been shown in the past year in the relation between hemorrhagic conditions and deficiency states The importance of vitamin C has already been emphasized That other factors may be significant was reported by Dam¹²⁹ in 1935, since he noted a hemorrhagic tendency resembling scurvy in chicks, not prevented by administration of cevitamic acid but produced apparently by a fat-soluble substance which he called vitamin K Almquist and Stokstad¹³⁰ have reported that this vitamin is present in the fecal matter of chicks which are not receiving this factor in the diet and have expressed the belief that it is probably synthesized to some extent in the lower portion of the intestinal tract The action of this substance, which occurs particularly in green vegetables, pig liver fat, hemp seed and alfalfa, most likely is attributable to the reduced content of prothrombin in the blood of chicks which are deficient in the substance, according to Dam and his associates¹³¹ and to Schønheyder¹³² The clotting time can be restored to normal in three days by administration of

127 Currie, D W Vitamins for Habitual Abortion, *Brit M J* **1** 752 (April 11) 1936

128 Rowlands, I W, and Singer, E Gonadotropic Activity of the Pituitaries of Vitamin E Deficient Rats, *J Physiol* **86** 323-326 (March 9) 1936

129 Dam, H The Antihaemorrhagic Vitamin of the Chick, *Biochem J* **29** 1273-1285 (June) 1935

130 Almquist, H J, and Stokstad, E L R Factors Influencing the Incidence of Dietary Hemorrhagic Disease in Chicks, *J Nutrition* **12** 329-335 (Oct) 1936

131 Dam, Henrik Schønheyder, Fritz, and Tage-Hansen, Erik Studies on the Mode of Action of Vitamin K, *Biochem J* **30** 1075-1079 (June) 1936

132 Schønheyder, Fritz The Quantitative Determination of Vitamin K *Biochem J* **30** 890-896 (May) 1936

the substance in which the animal is deficient. In rabbits Quick¹³³ has produced a hemorrhagic tendency with reduction of prothrombin by feeding spoiled sweet clover hay. He has expressed the belief that such hay contains a toxic substance which either destroys prothrombin or inhibits the mechanism by which the body produces this clotting factor and that alfalfa exerts a curative effect by supplying an accessory factor not identical with, but possibly related to, vitamin K and required by the organism for synthesis of prothrombin.

The importance to man of vitamin K, or of the related factor reported by Quick, has not been noted. Attention should be directed toward the possible rôle of these factors in the hemorrhagic tendencies of man.

THE OCCURRENCE OF OTHER ESSENTIAL FOODSTUFFS

Each year sees the reports of substances considered essential for normal nutrition and not included in the present list of vitamins or minerals. Two such reports in the past year suggested new dietary essentials. Elvehjem and his collaborators¹³⁴ in their experiments with rats identified a water-soluble, heat-labile factor, now called "alcohol-ether precipitate factor," distinct from any of the known dietary essentials. In the absence of this factor complete failure of growth of rats results, and the authors expressed the belief that this factor may explain the difficulty which previously has been encountered in the use of synthetic rations. A fat-soluble substance has been found by Goettsch and Pappenheimer¹³⁵ to be essential for chicks; they have found that absence of this substance leads to lesions of the nervous system. While the deficiency state produced is similar to that resulting from absence of vitamin B₄, this new factor is fat soluble, whereas vitamin B₄ is water soluble.

Zinc—Evidence that zinc is indispensable for rats has been demonstrated by Elvehjem and his colleagues¹³⁶. Lack of this metal leads to retardation of growth and interference with development of a normal coat of hair. In man the only definitely known relationship of zinc to health is in its relation to the prolongation of action of insulin.

Iron—Anemia attributable to nutritional deficiency of iron is of common occurrence. Murphy¹³⁷ has emphasized the fact that hypo-

133 Quick, A. J. The Coagulation Defect in Sweet Clover Disease and the Hemorrhagic Chick Disease of Dietary Origin, *Am J Physiol*, to be published.

134 Elvehjem, C. A., Koehn, C. J., Jr., and Oleson, J. J. A New Essential Dietary Factor, *J Biol Chem* **115** 707-719 (Oct.) 1936.

135 Goettsch, Marrienne, and Pappenheimer, A. M. A New-Found Diet Factor, *Science (supp.)* **84** 7 (Aug. 28) 1936.

136 Elvehjem, C. A., and others, cited in Nutritional Significance of Zinc, editorial, *J A M A* **106** 1011-1012 (March 21) 1936.

137 Murphy, W. P. Deficiency States—Anemia, *J Am Dietet A* **11** 406-410 (Jan.) 1936.

chronic anemias are true deficiency diseases and are attributable to an inadequate supply or inadequate utilization of iron. This may come about as a result of loss of iron, as in cases of chronic hemorrhage, from insufficient intake or absorption, or from unsatisfactory utilization, about which little is understood.

In their studies of the utilization of iron in experimental anemia of dogs, Whipple and Robscheit-Robbins¹³⁸ have come to the conclusion that iron given intravenously will return quantitatively as newly formed hemoglobin on the basis of 10 mg of iron for 3 Gm of hemoglobin. The influence of iron when given by mouth on production of hemoglobin is not proportional to the dose. The optimal dose of iron (40 mg per day for two weeks, or 560 mg) gives a return of about 55 Gm of hemoglobin and amounts to 35 per cent utilization. With larger doses of iron, for example, 400 mg daily, the daily output of about 95 Gm of hemoglobin represents about 5 per cent utilization. These observers found that iron salts are utilized with equal facility by the dog to produce hemoglobin when given by mouth in the ferrous, ferric or reduced state. The determining factor is the amount of metallic iron. Interesting studies on the absorption of iron in the dog have led Scheunert and Bruggemann¹³⁹ to the conclusion that reduced iron is absorbed better than is iron in colloidal form. In their dogs with ileal fistulas they found that more than 66 per cent of the iron given in various preparations was usually absorbed.

Interference with absorption of iron by some patients who have achlorhydria has been known to be a cause of hypochromic anemia. Apparently the hydrochloric acid in gastric juice is an important aid in absorption of iron. In this connection the studies of Kellogg and Mettier,¹⁴⁰ on the effect of alkaline therapy in relation to utilization of dietary iron and to regeneration of hemoglobin in cases of peptic ulcer, are worthy of note. While they studied only a small number of patients, the results indicated clearly that the bone marrow of patients undergoing alkaline therapy failed to respond to the ingestion of dietary iron as determined by production of hemoglobin. When the alkaline regimen was discontinued, increase in the concentration of hemoglobin occurred. In contrast, increase in the number of erythrocytes and reticulocytes occurred soon after the addition of iron-rich diets to the alkaline regimen. The likely conclusion is that alkalin-

138 Whipple, G. H., and Robscheit-Robbins, F. S. Iron and Its Utilization in Experimental Anemia, *Am J M Sc* **191** 11-24 (Jan) 1936

139 Scheunert, A., and Bruggemann, J. Ueber Eisenresorption bei Ileumfistelhunden, *Nutrition Abstr & Rev* **5** 1031-1032 (April) 1936

140 Kellogg, F., and Mettier, S. R. Effect of Alkaline Therapy for Peptic Ulcer on Utilization of Dietary Iron in the Regeneration of Hemoglobin, *Arch Int Med* **58** 278-284 (Aug) 1936

zation of the upper part of the gastro-intestinal tract interferes with utilization of dietary iron for the synthesis of hemoglobin but not with the utilization of material necessary for the formation of the stroma of erythrocytes

The success with which iron can be used in the prevention of hypochromic anemia during pregnancy is suggested by the observations on 200 women during the last four months of pregnancy by Corrigan and Strauss¹⁴¹ Twenty-four of 100 patients to whom iron was not given had values for hemoglobin of less than 70 per cent post partum On the other hand, none of the 100 women who received 0.5 Gm of ferrous sulfate daily during the last four months of pregnancy had less than 70 per cent of hemoglobin post partum

PREGNANCY AND LACTATION

In an interesting review of recent work on dietetics in which the attempt was made to correlate and assess requirements for various dietary essentials during pregnancy and lactation, Garry and Stiven¹⁴² pointed out certain conclusions which should be of practical value in the future It was clearly emphasized that present knowledge does not permit categorical statement of the amounts of the various dietary essentials which are required for correct nutrition during these periods of physiologic activity General principles are still the guide-posts However, standards have been set by the League of Nations Health Committee (Technical Commission),¹⁴³ and although these standards are high, they are probably necessary, and, as the authors pointed out, the evidence from dietary surveys indicates that many dietaries may fall far below these standards Since during pregnancy and lactation the maternal organism is subjected to special demands which, in a sense, may be considered efficiency tests, it seemed logical to Garry and Stiven that dietary deficiencies in a population are likely to be evidenced more clearly among pregnant and nursing women than among the general adult population From the practical standpoint, as McIlroy¹⁴⁴ has intimated, the real solution lies in the kitchen rather than in the laboratory or hospital ward

The collected data indicate that under ordinary circumstances diet has little effect on birth weight, this seems to depend more on the

141 Corrigan, J. C., and Strauss, M. B. The Prevention of Hypochromic Anemia in Pregnancy, *J. A. M. A.* **106** 1088-1090 (March 28) 1936

142 Garry, R. C., and Stiven, D. A Review of Recent Work on Dietary Requirements in Pregnancy and Lactation, with an Attempt to Assess Human Requirements, *Nutrition Abst. & Rev.* **5** 855-887 (April) 1936

143 Technical Commissioner's Report on Physiological Bases of Nutrition, League of Nations Health Committee, quoted by Garry and Stiven¹⁴²

144 McIlroy, L., and others. Discussion on Diet in Pregnancy, *Proc. Roy. Soc. Med.* **28** 1385-1406 (Aug.) 1935

growth impulse of the child and on the mother's constitution than on the mother's intake of food. Little information is available about the effect of variation in protein content of the diet in pregnancy. The impression seems to be general that excess of proteins, or of particular proteins, is harmful, and restriction of intake of meat is advised rather widely during pregnancy. Strauss¹⁴⁵ has produced evidence that a diet low in protein may in some cases be the cause of toxemia of pregnancy. He has reported successful treatment in some cases with a diet high in protein supplemented by vitamin B₁ and liver. The Technical Commission (League of Nations) has advised an intake of protein during pregnancy of 2 Gm for each kilogram of body weight, which seems high, in the early stages of pregnancy. The requirement of iron during pregnancy is variable. A variety of factors, such as vomiting and interference with absorption from hypacidity, may alter the requirement. Macy and Hunscher¹⁴⁶ estimated the desirable intake as 20 mg of iron a day, and Coons and Coons¹⁴⁷ discovered that the addition of wheat germ to a diet already providing 20 mg of iron a day greatly increased the storage of iron. The League of Nations (Technical Commission) has recommended the use of 1 quart (1,000 cc) of milk daily to satisfy the calcium requirement of the pregnant woman. For lactating women the commission has recommended 2 Gm of calcium daily. The requirement for vitamins is difficult to establish, but the commission has recommended 9,000 U S P units of vitamin A, from 150 to 250 international units of vitamin B, from 870 to 1,120 international units of vitamin C and 340 U S P units of vitamin D both during pregnancy and during lactation.

THE FREQUENCY, RECOGNITION AND TREATMENT OF DEFICIENCY STATES

In the review last year⁶⁰ some of the interesting phases having to do with the problem of nutrition of the people as a whole were discussed with particular reference to malnutrition, the influence of the economic depression on dietary habits and intake and the potentialities of an adequate diet with reference to the individual and the

145 Strauss, M G. Observations on the Etiology of the Toxemias of Pregnancy. Relationship of Nutritional Deficiency, Hypoproteinemia, and Elevated Venous Pressure to Water Retention in Pregnancy, *Am J M Sc* **190** 811-824 (Dec) 1935

146 Macy, I G, and Hunscher, H A. An Evaluation of Maternal Nitrogen and Mineral Needs During Embryonic and Infant Development, *Am J Obst & Gynec* **27** 878-888 (June) 1934

147 Coons, C M, and Coons, R R. Some Effects of Cod Liver Oil and Wheat Germ on the Retention of Iron, Nitrogen, Phosphorus, Calcium and Magnesium During Human Pregnancy, *J Nutrition* **10** 289-310 (Sept) 1935

race As knowledge advances a much clearer conception is being gained of the qualitative and quantitative dietary requirements of man However, the problem is a much greater one than simply an understanding of such requirements, for, as was pointed out in a recent interim report of a League of Nations committee,¹⁴⁸ agricultural, economic and health aspects are equally important It is stated that "the evidence that inadequacy of diet is widespread is conclusive, malnutrition is manifest in prevalence of rickets, scurvy, poor musculature, teeth of poor structure, anemia, chronic fatigue, poor condition of the skin, and sub-normal growth and weight to mention the most easily observable symptoms" Emphasis is placed on the well known fact that protective vitamin-containing foods are expensive and, therefore, from the economic standpoint the greatest single cause of defective nutrition is poverty The importance of nutrition as a part of medicine is clearly demonstrated by the establishment of a section of nutrition by the British Medical Association

The influence of the depression on the nutrition of the American people has been analyzed recently by McLester¹⁴⁹ He has approached the problem from the standpoint of "(a) the weight and the increment of gain among school children, as recorded before and after the depression, (b) the weights of the employed and unemployed among working men together with estimates of fitness, (c) the testimony of welfare agencies, and (d) the clinical observations of a selected group of physicians" He expressed the belief that, on the whole, the figures suggested that the nutritive state of the American school child has not suffered during the depression and that there has been no widespread undernutrition among the general population The incidence of deficiency diseases, as observed by a group of clinicians throughout the country, shows slight if any increase, with the possible exception of a few areas McLester expressed the belief that these good results are largely attributable to education

While it seems evident that the incidence of clearly recognizable deficiency states has not increased appreciably, there has been much discussion of the incidence of occurrence of partial deficiencies, the diagnosis of which depends in large part on keen and critical observations, on chemical or pathologic studies and on other laboratory methods Minot¹⁵⁰ expressed the belief that such borderline states of nutritional instability are more common than usually is appreciated, since there is a wide zone between optimal nutrition and the level

148 The Problems of Nutrition, editorial, *Brit M J* **2** 396 (Aug 22) 1936

149 McLester, J S Influence of the Depression on the Nutrition of the American People, *J A M A* **106** 1865-1869 (May 30) 1936

150 Minot, G R Nutrition and Deficiency Disease, *New York Times*, Sept 15, 1936

at which classic symptoms of recognized deficiency states develop. The use of chemical methods, particularly of those which permit estimation of the vitamin content of the urine, blood and other tissues, opens up an entirely new field in the recognition of deficiency states, although interpretation of results is still of questionable diagnostic significance.

In each section earlier in this review note has been made of methods of recognizing specific deficiency states. It is important to remember that deficiency states may occur alone or in association with other diseases, that a carefully taken dietary history may be of considerable value and that, with the use of pure preparations of vitamins, a therapeutic trial may aid in establishing the diagnosis.

In his efforts to recognize deficiency states the clinician must pay particular attention to the types of patients who may be expected to suffer from such conditions. Deficiencies may result from a variety of causes other than an inadequate diet. All the following factors may be significant in predisposing to deficiency: increased requirements during periods of rapid growth, pregnancy, infections and fever and when the metabolic rate is elevated, loss of abnormal quantities of essential substances (for example, by vomiting or diarrhea), impaired or altered gastro-intestinal function, and alteration in the metabolism of the vitamins (for example, in storage, destruction and utilization). Of these various factors, the most important from the standpoint of frequency are a diet that is inadequate because of poverty, because of faddism or, at times, because of treatment of disease and alteration in gastro-intestinal function (see the following comment).

In the treatment of deficiency states the most important factor is a well balanced, adequate diet which can be supplemented when necessary by preparations containing vitamins in concentrated form. Too much emphasis cannot be placed on the value of giving vitamins in a natural state. This is particularly true in relation to components of the vitamin B complex. Crystalline preparations of vitamin B₁ are of undoubted value in specific conditions, but because of the uncertainty of the number of components of the vitamin B complex which are necessary for normal health, it seems wise to supplement in most cases and except under conditions of experiment, the administration of the crystalline product with preparations such as brewers' yeast or wheat germ, which contain all the essential components.

If vitamin preparations can be successfully given orally, this seems the most desirable method of administration because it approaches the normal. Intramuscular and intravenous routes of administration have given more rapid response in some cases. The minimal require-

ment of each vitamin has not been clearly established, and experience has shown the wide zone which may exist between minimal and optimal requirements. Optimal levels are probably ideal levels. For therapeutic purposes, doses much larger than optimal requirements may be used. So far as is known, vitamin D is the only vitamin which in large doses can produce toxic effects.

Vitamin A can be administered in a variety of foods, either those which contain the elements in the form of the vitamin or as carotene. Carotene is not as well absorbed as vitamin A, and consequently in most circumstances the vitamin is the more satisfactory preparation to use. Preparations of vitamin A for parenteral use have not proved satisfactory, but crystalline carotene can be used as a substitute. Fish liver oils, particularly those of the halibut, cod and burbot, are rich sources of vitamin A for therapeutic use.

The vitamin B complex can be given in the form of brewers' yeast or wheat germ. Concentrates of vitamin B₁, liver extract, which is high in vitamin B₂ (G) content, and crystalline vitamin B₁ (now synthetically prepared) are all useful. The crystalline preparation can be used parenterally in therapeutic doses of from 10 to 20 mg daily. In the treatment of pellagra Spies¹⁵¹ has emphasized the importance of giving large doses of yeast or wheat germ and has recommended from 75 to 100 Gm daily.

Vitamin C can be given in the form of citrus fruit or tomato juice or in crystalline preparations by mouth or intravenously. The daily requirement lies probably between 30 and 50 mg, and therapeutic doses range from 50 to 200 mg daily.

For the child the Council on Foods of the American Medical Association recommends the daily use of 2 teaspoonfuls of cod liver oil (N. N. R., 1936) for a satisfactory intake of vitamins D and A. Irradiated milk, viosterol and irradiation of the skin are all good therapeutic sources of vitamin D. For dosages reference may be made to the articles of Jeans and of Shelling and Hopper. The Council on Pharmacy and Chemistry of the American Medical Association¹⁵² has taken a firm stand against the use of "shotgun vitamin therapy." Absence of evidence of the value and safety of such preparations and the frequent lack of necessity of taking them are emphasized. Shoddy diagnosis and treatment of actual and suspected deficiency disease should, by all means, be avoided if rapid and clearcut progress is to be made in this important field.

151 Spies, T. D. Treatment of Pellagra, *J. A. M. A.* **104** 1377-1380 (April 20) 1935.

152 Shotgun Vitamin Therapy, report of Council on Pharmacy and Chemistry, *J. A. M. A.* **105** 1037-1038 (Sept. 28) 1935.

THE GASTRO-INTESTINAL TRACT IN RELATION TO
DEFICIENCY DISEASES

The relationship between gastro-intestinal disturbances and deficiency states may be a reciprocal one. It has been clearly established that abnormalities of the tract may lead to deficiency states, and it is equally certain that deficiency states may lead to pathologic changes in the gastro-intestinal tract. Under certain conditions it is not clear which of the two comes first in a given case or whether they may be independent parts of the clinical picture.

Alterations in gastro-intestinal function which may produce a deficiency state have been classified by Wilbur and Snell¹⁵³ as follows: (1) inadequate intake of food (attributable to anorexia, incomplete diet and so forth), (2) loss of essential secretions or of food (attributable to vomiting, diarrhea or external fistula), (3) lack or decreased production of essential substances (for example, of hematopoietic factors, bile and digestive juices), and (4) inadequate intestinal absorption (attributable to obstruction, short-circuiting produced by a gastro-intestinal fistula, atrophy or disease of the intestinal mucosa).

Numerous cases illustrating these points have been reported in the past year. Perhaps the most interesting have to do with the influence of lack of bile on the absorption of vitamin A (see section on vitamin A). Bissell and Andrews¹⁵⁴ have made extensive studies of acholic cachexia in dogs and have reported that anemia, osteoporosis and gastroduodenal ulceration did not develop. The lives of the dogs were not prolonged by subcutaneous administration of vitamin D. The investigators concluded that acholic cachexia is not attributable to absence of bile from the intestinal tract, with consequent inability to absorb any specific food or vitamins. Klodt expressed the belief that bile facilitates absorption of vitamin C in the small bowel by considerably retarding oxidation of dilute solutions of vitamin C.

The effect of achlorhydria on gastro-intestinal function has been widely explored. In the past year Einhauser has pointed out that utilization of test doses of vitamin C by patients with achlorhydria is disturbed because of inadequate absorption. With Schroeder he reported a case of pernicious anemia with pigmentation of the face unaffected by treatment for pernicious anemia but promptly corrected by 300 mg of cevitic acid given intravenously each day for fourteen days.

There has been much discussion of the effects on the gastro-intestinal tract of deficiency states. Much of the work reported has

153 Wilbur, D. L., and Snell, A. M. Unpublished data.

154 Bissell, A. D., and Andrews, E. Acholic Cachexia. Experimental Studies, Arch Surg **32** 624-668 (April) 1936.

been based on animal experiments. Attempts to prove nutritional deficiency as an etiologic factor of such conditions as peptic ulcer generally have met with failure. Hurst¹⁵⁵ stated that he had never found any evidence for a nutritional origin of a gastro-intestinal disease in England. Stepp¹⁵⁶ gave the opinion that deficiency of vitamin A may lead to a reduced hydrochloric acid content of gastric juice, interference with absorption and diarrhea. McCarrison¹⁵⁷ expressed the belief that vitamin A deficiency leads to infections in the digestive tract. A summary of the effect of deprivation of vitamin A on the gastro-intestinal tract was presented by Robertson¹⁵⁸. The close relationship which may exist between components of the vitamin B complex and digestive function is illustrated by the accompanying atrophy of the papillae of the tongue, anorexia, achlorhydria and hypotonicity and hypomotility of the musculature, particularly of the small intestine. In a study of the effect of vitamin B₁ deficiency on the gastric juice of 2 healthy subjects, Alvarez and his co-workers did not find definite changes in concentration of hydrochloric acid or pepsin after six weeks (vitamin-calory ratio of 1.2 instead of Cowgill's minimum normal of 1.8). Villaret and his associates,¹⁵⁹ in their study of the character of gastric disorders in the course of alcoholic polyneuritis, found achlorhydria and hypochlorhydria with atrophic gastritis to be not uncommon. Improvement in these abnormalities preceded improvement of the neuritis after treatment was instituted. In rats Simpson could not find atrophy, ulceration or erosion of the gastric mucous membrane in vitamin B₁ deficiency. He expressed the belief that many of the variable reports in the literature are attributable to lack of uniformity in choice of animals and in dietary standards. Changes in enzymes which may accompany vitamin B deficiency have been incompletely studied. Kik, Sure and Buchanan have noted interesting changes which have been reported previously in this review (see section on vitamin B complex). Little is known of the effect of vitamin B₂ (G) deficiency on the intestinal tract, although the presence of the vitamin is thought to be necessary to maintain the mucosa in normal condition. Absence of vitamin C was reported by McCarrison to lead to congestion, hemorrhage and ulcerating lesions.

155 Hurst, A. F., quoted in discussion on Nutrition in Health and Disease, *Lancet* **2** 260-262 (Aug. 1) 1936.

156 Stepp, W. Vitaminmangel als Ursache und Folge von Magen-Darmerkrankungen, *München med. Wchnschr.* **83** 1119-1123 (July 10) 1936.

157 McCarrison, Robert. Nutrition in Health and Disease, *Brit. M. J.* **2** 611-615 (Sept. 26) 1936.

158 Robertson, Elizabeth C. Recent Work on the Tissue Changes in Vitamin "A" Deficiency, *Am. J. M. Sc.* **192** 409-436 (Sept.) 1936.

159 Villaret, M., Moutier, F., Justin-Besançon, L., and Klotz, H. P. Special Character of Gastric Disorders in Course of Grain Alcohol Polyneuritis, *abstr., J. A. M. A.* **107** 1346 (Oct. 17) 1936.

The remarkable effect of liver extract on hematopoietic function constitutes the outstanding therapeutic value of this substance in pernicious and other macrocytic anemias. That substances in liver extract may influence also gastro-intestinal function has not been well recognized. In a recent report Jones, Benedict and Hampton¹⁶⁰ noted the gastroscopic, surgical and roentgenologic observations which they made in a group of 5 patients with pernicious anemia. Following successful specific therapy of pernicious anemia, evidence of atrophy or hypertrophy of the gastric mucosa tended to disappear, Jones, Benedict and Hampton expressed the belief that this effect was attributable not only to increased blood supply but also to epithelial change associated with successful treatment of a specific deficiency state, rather than to healing of a chronic inflammatory process. In an equally interesting paper, Miller and Rhoads¹⁶¹ reported studies of the small intestine of a patient who had sprue without anemia. Following injection of liver extract there was a return toward normal form and function of the intestine, as was evidenced by roentgenologic study as well as disappearance of symptoms. It is suggested that liver extract administered parenterally conditions the functional activity of the small intestine. These reports are of particular interest because they tend to substantiate the belief of some workers that a close relationship exists between the hematopoietic factor of pernicious anemia and a factor similar to vitamin B₆ but that the two are not identical.

The oral complications of chronic alcoholism which may be wholly or in part of nutritional origin have been discussed by Blankenhorn and Spies and have been noted previously in this review.

Although knowledge of intestinal absorption is still meager, attention is called to studies noted previously in the review which have to do with absorption of carotene, interference with absorption of vitamin A in pregnancy, absorption of vitamin B₁ in dogs, absorption of vitamin D administered to infants in a variety of mediums and absorption of iron, particularly as it may be influenced by simultaneous administration of alkalis. Interference with absorption of vitamin C in achlorhydria also has been noted.

In experimental work Irwin, Steenbock and Kemmerer¹⁶² have observed that rats with avitaminosis (from lack of vitamins A, B

160 Jones, C M, Benedict, E B, and Hampton, A O. Variations in the Gastric Mucosa in Pernicious Anemia. Gastroscopic, Surgical and Roentgenologic Observations, *Am J M Sc* **190** 596-610 (Nov) 1935.

161 Miller, D K, and Rhoads, C P. The Effect of Liver Extract on the Small Intestine of Patients with Sprue, *Am J M Sc* **191** 453-456 (April) 1936.

162 Irwin, Margaret H, Steenbock, H, and Kemmerer, A R. The Influence of Vitamins A, B, or D, Anemia or Fasting upon the Rate of Fat Absorption in the Rat, *J Nutrition* **12** 357-364 (Oct 10) 1936.

or D) absorbed fat less rapidly than normal, but this was interpreted as a nonspecific effect. The addition of these vitamins to the diet of normal rats did not increase their ability to absorb fats.

Attention should be called to interesting studies which have been made on the nature and relationship of sprue, idiopathic steatorrhea, celiac disease and pernicious anemia. There is still much disagreement as to the nature of the intestinal, histopathologic and physiologic changes in these diseases. It is not possible to discuss in detail all the evidence which has been presented in this controversy, and it is suggested that reference be made to the original articles. Castle and his associates,¹⁶³ in an excellent study of 90 patients with sprue observed in Puerto Rico and Boston, pointed out that sprue, pernicious anemia and pellagra have many similar features, especially as regards the blood, gastro-intestinal system and nervous system. They suggested that sprue is a deficiency disease closely related to pernicious anemia and that lack of intrinsic or extrinsic factors or failure of absorption of them is a significant etiologic factor. Deficiency of iron in the diet also may be a factor.

On the other hand, Fairley,¹⁶⁴ who has studied 450 patients with tropical sprue in London and elsewhere throughout the world, expressed the belief that the disease is essentially different from pernicious anemia, celiac disease and idiopathic steatorrhea. He found sprue to affect many well-to-do persons who had been on an adequate diet, and he observed at postmortem examination no specific degeneration or inflammatory change in the intestine. He expressed the opinion that the phenomena of tropical sprue may best be explained in terms of a metabolic breakdown of the gastro-intestinal tract, characterized by defective absorption in the small intestine, with or without defective secretion of Castle's intrinsic factor. There is marked failure to absorb fat and often dextrose, moreover avitaminosis, when it occurs, is a secondary phenomenon dependent on malabsorption or on a too restricted diet, self-imposed with the object of cure. The disease responds to limitation of fat and administration of calcium without vitamin D. Further evidence of impairment of carbohydrate metabolism in celiac disease has been presented by Ross,¹⁶⁵ who has shown that liver extract may significantly influence carbohydrate metabolism by a factor possibly identical with Himsworth's "insulin-kinase."

163 Castle, W. B., Rhoads, C. P., Lawson, H. S., and Payne, G. C. Etiology and Treatment of Sprue, *Arch. Int. Med.* **56** 627-699 (Oct.) 1935.

164 Fairley, N. H. Tropical Sprue with Special Reference to the Intestinal Absorption, *Tr. Roy. Soc. Trop. Med. & Hyg.* **30** 9-32 (June) 1936.

165 Ross, C. W. Intestinal Absorption in Coeliac Disease, with Some Remarks on the Effect of Liver Extracts upon Carbohydrate Metabolism, *Tr. Roy. Soc. Trop. Med. & Hyg.* **30** 33-50 (June) 1936.

Book Reviews

Röntgenkymographische Bewegungslehre innerer Organe By Pleikart Stumpf, M D, H H Weber, M D, and G A Leltz, M D Price, 42 marks Pp 516, with 447 illustrations and 1 celluloid grid Leipzig Georg Thieme, 1936

This book was written mostly by Stumpf, in other words, he was not merely the editor. In the first 43 pages he takes up a discussion of what roentgen kymography is, the methods of using it and the apparatus for taking kymograms and for viewing and measuring them. He measures not only outlines but also variations in density, so that a time curve of the alteration of the thickness of an organ may be obtained. He explains the distinction between surface kymography made with the grid moving and staircase kymography made with the film moving. He points out that each method has its uses. The rest of the book is taken up with a discussion of the uses of kymography for diagnosis in various parts of the body.

There are about 120 pages devoted to the heart in health and disease, and the movements of the heart are analyzed with regard to time and extent. Many of Stumpf's kymographs are timed by electrocardiograms. He gives statistical averages for various chambers for various ages. He also considers the effect of respiration.

One chapter is devoted to the shape of the kymographic curve for various disease conditions, and an explanation is given for each form. However, on the whole the chapter seems empirical rather than theoretical, and it appears to be extremely practical.

There is a 10 page chapter on the pulsations transmitted to other organs than the chest, and then Weltz gives 30 pages on the thoracic aorta, which he considers a mere beginning of the study. He also goes further into the matter of the effect of respiration on the movement of the heart. This chapter overlaps somewhat a briefer discussion by Stumpf on pages 81 to 88.

Bohme gives 20 pages on a most interesting study, mostly experimental studies on animals, of the movements of the chambers and vessels and of the blood within them. The demonstration was made by the injection of colloidal thorium diiodide and sometimes iodized poppy-seed oil into the blood stream. It seems to me that this is a valuable method for investigations in physiology.

Weber gives 35 pages of discussion on the movements of the diaphragm, ribs, lobes of the lungs and bronchi in normal respiration.

Weltz contributes a 20 page discussion of pathologic respiration, especially in asthma.

Dong devotes 50 pages to respiration in the presence of disturbed musculature or innervation and in the presence of tumors of the lungs. I received the impression that this field of clinical investigation is difficult. It is hard for me to evaluate which of his results may be clinically useful and which are only interesting demonstrations of the roentgen kymograph. Disturbances by infiltrations and by interlobar pleural adhesions can be brought out in this and apparently in no other way.

Von der Weth gives a 32 page report on alterations in the breathing mechanism in pulmonary tuberculosis. It seems possible that this information, attainable by no other method than roentgen kymography, may be of great importance as a guide to therapy, for instance, by showing the effect of interlobar adhesions in transmitting diaphragmatic movement into the upper lobe of the lung. The demonstration of such an effect in a patient might easily be the determining consideration in deciding on section of the phrenic nerve.

There are 13 pages by Schoen on substernal goiter alone.

The alimentary tract receives only 80 pages. I expect that this section will be considerably expanded in the future, although in this region, where movements are usually slow enough to be followed with the eye on the fluoroscopic screen,

I do not know how essential kymography may become for diagnostic purposes. There is a 24 page chapter by Dahm on the esophagus. The rest of the discussion of the stomach and duodenum is by Stumpf himself. The analysis of peristaltic movements from roentgen kymograms is necessarily carried out in detail, for here where the movement consists of a peristaltic wave passing over a long organ, it is not as easy to recognize its true nature by means of a kymogram as it is in the case of the heart, where the pulsation is more of the organ as a whole.

Stumpf's discussions of the stomach and duodenum contain a good deal of investigation of normal physiology. This is, of course, absolutely essential as a background for understanding any pathologic disturbance of motility. It is still difficult to analyze the effects of the muscular coats and of the muscularis mucosae.

Twenty-five pages by Sack cover the urinary tract. Peristaltic movement in the ureter is beautifully demonstrated.

There is a closing chapter of 6 pages by Neeff in which he discusses the dangers from the heavy intensity of irradiation necessary to produce roentgen kymograms. These exposures fall well within the limits of what is safe. Nevertheless, if the ovaries or testes are in the field, a single roentgen kymogram might under some circumstances be as large an exposure as should ordinarily be undertaken, i. e., one should not advise a repetition of the examination. In the chest there is much more leeway, so that a good many roentgen kymograms can be taken of the heart and lungs without treading on ground that is at all dangerous.

On Deficiency of A Vitamin and Visual Dysaptation By C. Edmund and S. Clemmesen. Price, 5 kroner. Pp. 92. Copenhagen: Levin & Munksgaard, 1936.

A considerable portion of the principal essay in this brochure is devoted to a detailed and critical study of the method employed for the determination of the power of distinction and its use in the detection of visual dysaptation (nyctalohemeralopia). Using various Tscherning neutral filters and a series of Snellen letters (6/36) of different shades of gray, with Bouguer-Fechner fractions varying in geometric progression, these investigators determined the power of distinction (logarithm of the reciprocal value of the B-F fraction) at different levels of illumination for groups of hospital nurses, pregnant women, and male and female patients selected at random. Details are presented regarding the determination of correct B-F fractions represented by the gray letters used in order that powers of distinction may be indicated in absolute values, thereby making possible a comparison of the results of various investigators. A number of pages are devoted to the experimental technic, errors of the method, determination of the normal curve and limits of normal zone, seasonal variations and the influence of age.

The ensemble of apparatus and methods used by the authors are suitable and doubtless adequate for clinical investigations. Obviously, the findings by such methods are not to be regarded as determinations of the threshold of sensitivity to light, in which the foveal and peripheral retinal perception of light and the effects of adaptation may be determined. However, investigations by others indicate a reduction in function of the central parts of the retina as well as of the periphery for white and colored light in hemeralopia. To a certain extent visual acuity enters into the findings obtained by Edmund and Clemmesen and may give powers of distinction which are too low. In general, determinations of the minimum visible, examinations of visual fields at reduced illumination and determinations of visual acuity under reduced illumination are somewhat unsatisfactory clinically, since they tax the intelligence of the patient or are not sufficiently sensitive to detect slight hemeralopia. In certain respects, therefore, the determination of the power of distinction is the method of choice, since the estimation of how great the differences in brightness must be in order to be noticed is of importance in daily life.

The concluding portion of the essay and the appended article on the parenteral treatment with vitamin A of dysaptation (nyctalohemeralopia) in some pregnant women give details of treatment and tables of data regarding the power of distinction before and after the administration of vitamin A. A group of fifty-two

nurses in the Sundby Hospital, Copenhagen, were found to be normal in power of distinction, with a marked tendency to the lower limit of normalcy during the winter months. A preventive diet containing from 1,500 to 2,000 U S P units of vitamin A is suggested and emphasis is laid on the inclusion of sufficient vegetables in the diet during the winter months. Nearly half the forty-nine pregnant women tested for dysaptation showed a pathologic decrease in the power of distinction. Intramuscular injections of a vitamin A preparation (containing about 40,000 U S P units) produced a disappearance of dysaptation which lasted for about a week in the majority of cases. In general these investigations showed the correlation between vitamin A deficiency and reduction in the power of distinction and demonstrated the improvement of function produced by the administration of the vitamin.

Applied Dietetics for Adults and Children in Health and Disease By Sanford Blum, M D Price, \$4.75 Pp 408 Philadelphia F A Davis Company, 1936

Blum's book consists essentially of lists of foods which are advised for consumption and of foods which are to be avoided by persons with various conditions encountered in the practice of medicine. The author presents lists which are captioned so that the physician has merely to find in the index of the book the condition with which he is concerned and then turn to an already prepared list of foods for his patient. The presentation is divided into two parts, the first includes "Dietary for Adults in Health and Disease" and the second "Dietary for Infants and Children in Health and Disease." There are a general index and an index by foods. The diets are based on those the author employed "during a period of twenty years." No references are made to the literature.

Each diet is generalized. The foods are rarely expressed quantitatively and then only in general terms. Brief suggestions and discussions are made in regard to diets and habits of eating. While the diets are generalized in many respects, they are listed for specific types of patients and conditions. For instance, the author has a diet for "chronic indigestion in middle aged adults," for the "spare adult male—impaired digestion," for the "spinster with impaired digestion," for the "frail young mother," for the "professional man" and for the "frail woman school teacher," and there are many other diets specifically captioned. The author uses a different diet for treating obesity in a "woman thirty-five years old" and for treating it in a "two-hundred-and-sixty-pound female clerk." No logical reasons are presented to warrant such minute differentiation. The normal adult is advised to avoid such foods as duck, stew, tongue, goose, kidney, lobster, crab, beets, sprouts, sauces, gravies and many other foods which make up the average normal person's diet. If such commonly consumed foods are to be avoided, the author should at least present reasons. Again, he advises a "professional man" suffering from malnutrition to drink a "glass of water with a teaspoonful of salts, on arising." Why such a practice? The term salts is indefinite in itself.

The book contains a list of foods which leaves the reader wondering why any one of them is selected or eliminated. The diets as listed cannot be intelligently prescribed, nor can they aid the physician in understanding his diet problems. Such a list of foods fosters the use of diets for placebo rather than for therapeutic purposes. The book can be of little use to the medical profession.

La tension mediana dinamica By Angel Cammarota Pp 170 Buenos Aires El Ateneo, 1936

In this monograph Cammarota makes a complete study of the "mean arterial tension" in relation to health and disease. The mean arterial tension, as defined by the author, is that constant pressure which at a given time causes the body tissues to have the same energy as the variable tension in the vessels. That pressure, so described, has no relation to the arithmetical mean pressure (one-half the sum of the systolic and diastolic values), and in order to make a distinction it is called the mean arterial tension.

After a preliminary use of several instruments the author chose for his studies the spring oscillograph devised by Frank Soler, of Argentine, and found that the mean arterial pressure varied extensively in different subjects who were apparently in good health, consequently no definite standard figures could be obtained

Cammarota studied the mean arterial pressure in relation to aortic regurgitation, hypertension and hypotension, arrhythmia, aneurysm, vascular disturbance of the extremities and hyperthyroidism, presenting oscillograms taken at different intervals and complemented when possible with studies made months or even years after the original data were recorded. He arrived at the conclusion that the mean arterial tension has no particular bearing on the diagnosis or prognosis in diseases of the heart and circulatory system

The author found also that the mean arterial tension may vary considerably within a few minutes and established a definite relationship between it and the systolic and diastolic pressures, especially the latter. Cammarota attributes differences of opinion as well as many errors in experimental contributions to deficiency in the various instruments and devices now in use for studying this particular phase of the blood pressure

Exophthalmic Goiter and Its Medical Treatment By Israel Bram, M D
Foreword by R G Hoskins, Ph D, M D Second edition Price, \$6 Pp
456, with 79 illustrations St Louis C V Mosby Company, 1936

In this edition Bram has employed the same general plan as in the first edition (published in 1920) in presenting his subject. He has, however, increased the scope of each phase of the disease so as to include material that has developed since 1920. Considerably more material is devoted to laboratory tests and case histories. There are fifty-five case histories summarized in the last chapter. The cases were chosen from the author's files and are representative of his "personal experience with over five thousand cases of this disease observed within a period of twenty-five years." The author continues to adhere to medical treatment as the only satisfactory form of therapy for exophthalmic goiter.

The foreword to this edition was written by R G Hoskins, Director of Research, the Memorial Foundation for Neuro-Endocrine Research of the Harvard Medical School, who believes that "there is a legitimate place for the partisan in the better sense of the term"

The improvements make the book a good survey of the disease from a clinical standpoint. The author is an extremist on the medical treatment of exophthalmic goiter, but if the reader keeps that in mind when reading the book, he can derive a great deal of benefit from the discussion of the medical treatment of this disease. This is especially true for the radiologists and surgeons, who are inclined to neglect the medical and constitutional aspects of the disease when applying their forms of local therapy.

The Art of Treatment By William R Houston, M D Price, \$5 Pp 744
New York The Macmillan Company, 1936

This is a most interesting and attractive piece of work. The author has attempted to write so as to stimulate intelligent thinking along therapeutic lines, and certainly he has gone far toward accomplishing this aim.

This book is not a textbook on therapeutics in the ordinary sense, little emphasis being laid on drugs and their administration. However, a great deal of independent reasoning and homely philosophy are put forth to drive home the facts that in successful therapy the patient rather than his disease must be treated, that vastly more is *not* known concerning treatment than is known concerning it and, finally, when all is said and done, that most therapeutic conceptions and plans are simple—success turning largely on doing simple things well rather than on carrying out elaborate procedures inadequately.

The book is divided into seven parts, and by all odds the longest part is that which deals with psychotherapy. This long chapter is written sensibly and from an unprejudiced point of view. The entire book is well and clearly written, so

that it makes interesting reading throughout, it is full of valuable hints and suggestions. Surely a book of this type will have a successful career. Not only is it useful for reference purposes, but it affords pleasant reading. It is an admirable contribution toward describing what the art of medical practice amounts to. Medical students, practicing physicians and teachers will all enjoy it.

Endocrinology in Modern Practice. By William Wolf, M.D., Ph.D. Price, \$10. Pp 1018, with 252 illustrations. Philadelphia: W. B. Saunders Company, 1936.

In discussing another book on endocrinology in these columns several years ago the reviewer raised the question of whether any one man could deal adequately with this subject in its present state, it seemed then that the special knowledge of the trained gynecologist, internist, chemist, physiologist and biochemist which had to be synthesized was outside the scope of individual effort. That this point of view is on the whole sound is proved by the character of most of the endocrinologic texts: the books written by those who have worked on the experimental side are usually pitifully defective as to clinical discussion, while those written by clinicians insult the reader with a hash of pseudoscientific physiologic and chemical nonsense. Nevertheless, in the present instance Dr. Wolf has largely surmounted these objections and must be given full and free praise for having produced a really first class all-around book. The style is pleasant and lucid, the reasoning is conservative, the clinical descriptions are excellent and, above all, the summaries of fundamental physiologic knowledge of the endocrine glands are in the best possible accord with recent studies. Here at last is a safe and useful book, free from the "hokum" of the side-show.

Anales del centro de investigaciones fisiologicas. By Prof. Roque A. Izzo. Pp 175. Buenos Aires: La Semana Medical, 1935.

In the preface of this symposium on tuberculosis the ideals of Dr. Carlos A. Bruchman, senator and physician, are set forth. He conceived the idea of an institution in Buenos Aires the aim of which would be the study of tuberculosis not in general but as found in that community. He felt that such an institution should study the problems of tuberculosis with special reference to the particular social strata, geographic location, habits, foods and racial admixtures found in that particular community. He aptly expressed himself by saying "not tuberculosis in general but our tuberculosis" should be studied.

The fruit of his idea is this initial volume covering the years 1934 and 1935. Under the direction of Prof. Roque A. Izzo this first volume deals with the problems of tuberculosis found in the center. There are a considerable number of case reports, and these do not lack for illustrations of excellent quality. The results obtained with phrenicectomy and thoracoplasty compare well with results reported elsewhere. Other chapters of interest are those dealing with unusual cases of diabetes complicating tuberculosis and albuminuria in pulmonary tuberculosis. There are a considerable number of statistical tables.

The Thyroid. By E. P. Sloan, M.D. Price, \$10. Pp 475, with 99 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1936.

This handsome monograph is somewhat disappointing. Most of it is a compilation, put together in a rather uncritical and disjointed style, of material that is readily available in the current literature. One is given the impression that everything leads up to the chapter on surgery. Here technic and procedure are discussed in detail, and there are some excellent colored plates of the surgical anatomy of the thyroid region. The author properly stresses his own methods, but the final picture of the incision closed by clips, with a drain protruding from the center of the wound, is a shock to those familiar with Halsted's beautiful "silk technic." The reviewer fails to see the point of the reproduction on the title page of the bronze cast of Dr. Sloan's hands.

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RETENTION AND UTILIZATION OF ORALLY ADMINISTERED IRON

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IOWA CITY

Although there is a voluminous literature on both iron balances and hypochromic anemia, no systematic study has been made to determine the amount of iron retained by patients with anemia who recover after the administration of massive doses of iron. We wish to present the results of such studies of patients with hypochromic anemia who were given large amounts of iron by mouth.

The effectiveness of iron in the treatment of hypochromic anemia has been repeatedly demonstrated, and failure to obtain the expected therapeutic response is usually due to a complicating infection or to the employment of a suboptimal amount of iron. It has been recognized, however, that the intake of iron is greatly in excess of the amount retained or utilized by the body, and Heath,¹ in confirmation of this view, has shown that only 3.4 per cent of the iron administered orally is utilized in the production of hemoglobin during the period of recovery from anemia. A higher percentage of utilization was observed early in the period of recovery and also when small amounts of iron were administered. His results were obtained by comparing the intake of iron to the amount of iron in the new-formed hemoglobin, assuming that the blood volume was 5 liters in each patient. Heath, Strauss and Castle² found that with parenteral administration the percentage of the iron utilized in the formation of hemoglobin varied from 69 to 154, with an average utilization of 96 per cent, so that iron which is given by this route corresponds closely to the amount gained in the circulating

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This work was begun in association with Dr. C. W. Baldrige, who died on Nov. 22, 1934.

1 Heath, C. W. Oral Administration of Iron in Hypochromic Anemia, *Arch. Int. Med.* **51**: 459 (March) 1933.

2 Heath, C. W., Strauss, M. B., and Castle, W. B. Quantitative Aspects of Iron Deficiency in Hypochromic Anemia, *J. Clin. Investigation* **11**: 1293 (Nov.) 1932.

hemoglobin These results do not account for replacement of the diminished stores of iron in the body, and it seems reasonable to assume that at least a portion of the intake of iron is utilized for this purpose Hahn and Whipple³ have shown that the reserve storage of iron in the dog can be exhausted within two or three months by continuous anemia produced by withdrawal of the blood A similar depletion of the stores of iron is probable in the human being after a chronic loss of blood and possibly in idiopathic hypochromic anemia

It must be recognized that experiments on the iron balance do not furnish a complete story of the utilization and absorption of iron This method of study does not distinguish between that portion of the iron which passes unchanged through the gastro-intestinal tract and that which has been utilized and reexcreted into the bowel Methods for the quantitative determination of the iron content of food and excreta are numerous because none is perfect, and it was this lack of a uniformly acceptable method that led to much difficulty in the determination of the balances of iron when small amounts of this metal were involved In studies, such as we are presenting, in which the amounts of iron administered are very large, the usual sources of error are of less significance

METHODS

Iron and ammonium citrates was selected for use in this investigation because of its known potency in the treatment of these types of anemia It was administered as an aqueous solution of the brown scales, 15 grains (1 Gm) three times daily, equivalent to approximately 500 mg of metallic iron per day One patient (case 5) received a solution of the green scales, which contained a somewhat smaller amount of iron No distinction was made as to the presence or absence of hydrochloric acid in the gastric contents, since we were concerned primarily with the amount of iron retained and utilized by the body

Loss of menstrual blood was encountered in five of the nine women during the studies The amount of iron lost in the menstrual flow was regarded in the calculations as eliminated iron, so that the positive balances represent the iron retained in spite of this loss

The subjects selected for these metabolic studies were patients with a microcytic hypochromic type of anemia, and a brief summary of the clinical hematologic and laboratory data is given in tables 1 and 2 Balance periods were of six days' duration, and in each case the control period was preceded by a three day period of adjustment on the balance diet before observations were begun The balance periods ran continuously except in case 1, in which there was an interval of fifty days between the fifth and the sixth period and in case 2, in which there was an interval of twenty-four days between the third and fourth period Carmine was used to mark the stools at the beginning and at the end of each balance period

Three standard diets were adjusted to contain 1 Gm protein per kilogram of body weight and a caloric intake of about 150 per cent of the basal requirements

3 Hahn, P F and Whipple, G H Iron Metabolism Its Absorption, Storage and Utilization in Experimental Anemia, *Am J M Sc* **191** 24 (Jan) 1936

The ratio of acid to base in the diet was approximately 1:2:3. The compositions of the three standard diets, as found by analysis and by calculation from the tables of Rose,⁴ were almost identical, so that in computing the iron balances the iron in the food was determined by calculation from these tables rather than by analysis.

TABLE 1—Data for Patients with Anemia

Patient	Age	Sex	Diagnosis	Clinical Features
1	26	F	Hypochromic anemia, menorrhagia	Repeated severe uterine hemorrhages for 6 years, hemorrhage from temporal artery after an injury, hypochlorhydria
2	47	M	Hypochromic anemia, marginal ulcer	Peptic ulcer for 15 years with several severe hemorrhages, gastro enterostomy performed but bleeding persisted, koilonychia
3	46	F	Hypochromic anemia, menorrhagia	Menorrhagia for 4 years, relieved by application of radium 7 months before balance studies, hypochlorhydria
4	40	F	Hypochromic anemia, menorrhagia	Chlasmatic bleeding, dilation and curettage of uterus showed normal endometrium
5	37	F	Hypochromic anemia atrophic arthritis	No abnormal loss of blood, dysphagia, hypochlorhydria, atrophy of tongue, anemia more severe than in ordinary arthritis and responded to iron
6	38	F	Hypochromic anemia, steatorrhea	No abnormal loss of blood, frequent, profuse, bulky stools since age of 15, sore mouth and atrophic tongue, koilonychia, dysphagia, hypochlorhydria
7	39	F	Hypochromic anemia of pregnancy	Eight pregnancies, no abnormal loss of blood, hemoglobin, 55 per cent prior to last delivery
8	32	F	Hypochromic anemia (idiopathic)	No history of abnormal loss of blood, adequate diet, atrophic tongue, koilonychia, splenomegaly, hypochlorhydria
9	44	F	Hypochromic anemia (idiopathic)	Dysphagia, no abnormal loss of blood atrophic tongue, koilonychia latent syphilis, achlorhydria
10	35	F	Hypochromic anemia (idiopathic)	Dysphagia, atrophic tongue, no abnormal loss of blood achlorhydria

TABLE 2—Data for Patients with Anemia*

Patient	Hemo- globin, %	Hemato- crit, %	Erythro- cytes, %	Color Index	Volume Index	Saturation Index	Gastric Acidity	Basal Metabolic Rate
1	30	43	69	0.43	0.70	0.62	Low	-8
2	10	15	29	0.34	0.51	0.66	0	-1
3	54	69	109	0.50	0.60	0.78	0	-4
4	75	72	95	0.78	0.75	1.04	Normal	± 0
5	40	68	90	0.44	0.76	0.60	Low	-6
6	39	60	101	0.39	0.60	0.65	Low	-11
7	39	61	102	0.38	0.59	0.64	0	+7
8	42	68	84	0.50	0.80	0.62	Normal	+10
9	44	65	81	0.54	0.84	0.67	0	-6
10	32	52	76	0.42	0.68	0.62	0	-20

* The percentages were calculated from the normal values of Osgood (A Textbook of Laboratory Diagnosis, ed 2), Philadelphia, P. Blakiston's Son & Co., 1935, p. 420.

of the food. These diets were alternated during the six day periods. The food did not come in contact with metal during its preparation, except occasionally with aluminum. The drinking water, which contained less than 0.1 mg. of iron

4 Rose, Mary S. Laboratory Handbook for Dietetics, ed 3. New York, The Macmillan Company, 1929.

per liter, was not considered in calculating the balances. The iron content of the iron and ammonium citrates and other medications was determined by analysis. All excreta were carefully collected and stored in glass or porcelain-lined containers, and all possible precautions were taken to prevent contamination.

Nitrogen was determined by the Kjeldahl method and phosphorus by the method of Fiske and Subbarow.⁵ All determinations of iron were made in triplicate by the method of Reis and Chakmakjian,⁶ and the accuracy of this method was repeatedly verified by the recovery of added iron from representative specimens.

The hemoglobin content was determined by the Newcomer method⁷ and the hematocrit values by the method of Van Allen.⁸ Erythrocyte, leukocyte and reticulocyte counts and hemoglobin and hematocrit determinations were made daily or on alternate days. Differential leukocyte counts were made during each balance period.

RESULTS

The control periods in these cases are open to all the criticisms that obtain in iron balances under physiologic conditions. The diet contained from 9 to 12 mg of iron per day, and on this approximately normal intake six patients were in negative and four in positive iron balance. The patient who presented the lowest negative balance (patient 2) was losing a small amount of blood continuously from a gastrojejunal ulcer, which would tend to lower the iron balance and to account partially for this extremely low result. Patient 7 received 168.6 mg of iron by mistake on the last day of the control period and during the six day period retained 106.8 mg. She received the same diet which resulted in a negative or a slightly positive iron balance in the other patients, so that most, if not all, of the retained iron came from the single dose of iron and ammonium citrates.

Retention—With the administration of iron and ammonium citrates these patients retained a surprisingly large amount of iron. The complete results of the studies are given in table 3 and a summary of the retention of iron by periods in table 4. The first patient retained 6,760.5 mg of iron in forty-eight days, and patient 9 retained 8,854.4 mg in twenty-four days. The greatest retention occurred in the first and second periods of the administration of iron, with a decreased retention in the subsequent ones. In each of the second, third and fourth periods there was one patient in negative iron balance, but no patient presented this feature in more than one period. Patient 1, whom we

5 Fiske, C. H., and Subbarow, Y. The Colorimetric Determination of Phosphorus, *J. Biol. Chem.* **66**: 375 (Dec.) 1925.

6 Reis, F., and Chakmakjian, H. H. Colorimetric Method for Quantitative Determination of Iron in Blood in the Form of Dispersed Prussian Blue, *J. Biol. Chem.* **92**: 59 (June) 1931.

7 Newcomer, H. S. A New Optical Instrument for the Determination of Hemoglobin, *J. Biol. Chem.* **55**: 569 (April) 1923.

8 Van Allen, C. M. An Hematocrit Method. *J. Lab. & Clin. Med.* **10**: 1027 (Sept.) 1925.

TABLE 3—Summary of the Data

Patient	Period	Weight, kg	Nitrogen, Mg		Phosphorus, Mg			Iron, Mg		Erythro cytes, Millions	Hemo globin, Gm
			Intake	Excretion	Balance	Ingestion	Excretion	Balance	Ingestion	Excretion	Balance
1	1	52.5	10.90	12.28	-1.38	1.53	1.51	-0.02	10.0	19.9	-9.9
	2	52.4	11.52	10.87	+0.65	1.58	1.31	+0.27	516.1	477.9	+38.2
	3	52.3	11.93	12.74	-0.81	1.61	1.28	+0.33	16.1	252	+263.5
	4	52.7	11.47	10.59	+0.88	1.38	1.02	+0.36	516.1	559.6	-43.5
	5	53.1	11.49	10.35	+1.14	1.57	1.32	+0.25	516.1	481.7	+31.4
2	6*	53.1	11.49	12.91	-1.42	1.57	1.41	-0.13	516.1	446.9	+69.2
	7	55.0	11.52	12.55	-1.03	1.58	1.19	+0.39	516.1	211.8	+304.3
	8	55.2	11.61	10.79	+0.82	1.60	1.0	+0.30	516.2	251.7	+264.5
	9	56.2	11.62	8.63	+2.99	1.61	1.41	+0.20	516.2	320.2	+196.0
	1†	66.3	7.40	7.61	-0.21	1.05	0.99	+0.06	7.2	24.9	-17.7
3	2	68.6	7.08	7.89	-0.81	1.08	0.62	+0.46	513.5	419.9	+93.6
	3	69.5	9.05	7.04	+2.01	1.28	0.97	+0.31	514.7	351.7	+163.0
	4‡	68.1	18.69	12.62	+6.07	1.81	1.19	+0.62	522.0	184.2	+337.8
	5	68.8	18.58	12.52	+6.06	1.78	1.14	+0.64	522.6	361.0	+161.6
	6	69.0	9.22	8.89	+0.33	1.10	1.18	-0.08	9.1	19.9	-10.8
4	1	69.6	10.20	9.05	+1.15	1.18	1.17	+0.01	515.8	290.5	+225.3
	2	69.5	10.20	8.88	+1.32	1.18	1.16	+0.02	515.8	290.6	+225.2
	3	76.6	9.98	9.69	+0.29	1.19	1.12	+0.07	10.1	12.2	-2.1
	4	76.8	10.28	8.94	+1.34	1.19	0.85	+0.34	515.9	153.8	+362.1
	5	56.9	10.22	8.42	+1.80	1.49	1.03	+0.46	12.6	9.7	+2.9
5	1	57.2	11.14	8.29	+2.85	1.53	1.63	-0.10	478.1	187.4	+290.7
	2	60.0	11.18	9.62	+1.56	1.57	1.55	+0.02	477.8	317.1	+160.7
	3	59.5	10.20	8.50	+1.70	1.41	1.38	+0.06	476.7	219.7	+257.0
	4	59.2	10.18	9.91	+0.27	1.43	1.52	-0.09	476.8	581.2	-104.4
	5	52.0	9.89	9.92	-0.03	1.18	1.10	+0.08	38.1	18.6	+19.5
6	1	52.0	10.17	9.34	+0.83	1.18	1.07	+0.11	515.9	357.2	+158.7
	2	52.2	9.32	9.10	+0.22	1.10	1.09	+0.01	514.7	520.5	-5.8
	3	53.7	9.96	9.65	+0.31	1.16	1.21	-0.05	515.1	450.6	+64.8
	4	61.4	10.06	8.23	+1.83	1.16	1.11	+0.02	10.0	21.0	-11.0
	5	62.1	10.10	9.41	+0.69	1.15	1.14	+0.01	515.7	334.3	+181.4
7	1	45.0	7.38	7.78	-0.40	1.02	0.99	+0.03	12.7	12.5	+0.2
	2	44.1	9.27	9.04	+0.23	1.29	1.31	-0.05	519.2	527.5	+241.9
	3	48.8	9.54	8.41	+1.13	1.35	1.38	-0.03	519.1	527.1	+292.0
	4	80.9	9.79	11.1	-1.52	1.44	1.51	-0.07	11.9	11.8	+0.1
	5	80.3	10.95	9.87	+1.58	1.44	1.51	+0.23	517.1	185.7	+331.6
8	1	81.1	10.18	8.12	+2.06	1.41	1.03	+0.41	16.9	110.5	+106.1
	2	80.3	10.26	6.72	+3.54	1.47	1.03	+0.44	517.2	165.6	+351.6
	3	79.7	10.25	8.04	+2.21	1.67	1.03	+0.64	517.2	130.9	+386.3
	4	71.7	9.01	8.25	+0.76	1.08	0.99	+0.09	9.7	17.5	-7.8
	5	52.0	10.19	8.58	+1.61	1.19	0.80	+0.39	516.3	260.4	+255.9
9	1	51.9	10.07	9.15	+0.92	1.18	1.27	-0.09	516.2	215.8	+300.4
	2	51.5	10.19	9.33	+0.86	1.19	1.05	+0.14	516.3	267.3	+248.9
	3	51.8	10.20	9.36	+0.84	1.19	1.24	-0.05	516.7	277.2	+239.5
	4	51.8	10.20	9.36	+0.84	1.19	1.24	-0.05	516.7	277.2	+239.5
	5	51.8	10.20	9.36	+0.84	1.19	1.24	-0.05	516.7	277.2	+239.5

* There was a fifty day interval between periods 6 and 7
† There was a three day control period. All other periods were six days long
‡ There was a twenty four day interval between periods 3 and 4

were able to follow by means of metabolic studies for a total of nine six day periods, presented some interesting features. An interval of fifty days elapsed between the fifth and the sixth balance period, during which time the patient took iron and ammonium citrates, 45 grams (3 Gm.) daily, except for a lapse of three days. In spite of this prolonged period of administration of iron, she still showed a markedly positive balance during the subsequent metabolic studies, and during the period of observation alone she retained 676 Gm. of iron. How long these large amounts of iron are retained by the body we are unable to say, but the continued storage at the end of ninety-eight days of the administration of iron shows that it is more than a transient affair.

The experience with patient 6, who received iron on the last day of the control period, suggests that absorption and retention are rapid in spite of the delay that occurs in the response of the hemoglobin. It has

TABLE 4—Average Daily Iron Balances (Mg.) by Periods

Patient	Control Period	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7	Period 8	Total Iron Balance
1	-9.9	+38.2	+263.8	-43.5	+34.4	+69.2	+304.3	+264.5	+196	6,760.5
2	-17.7	+93.6	+153.0	+337.8	+161.6					4,535.5
3	-10.8	+225.3	+225.2							2,702.7
4	-2.1	+362.1								2,173.0
5	+2.9	+290.7	+160.7	+257.0	-104.4					3,624.4
6	+19.5	+158.7	-5.8	+64.8						1,305.0
7	-11.0	+181.4								1,058.2
8	+0.2	+241.9	+292.0							3,203.2
9	+0.1	+331.6	+406.4	+351.6	+356.3					8,854.4
10	-7.8	+255.9	+300.4	+248.9	+239.5					6,268.4
Average	-4.8*	+217.9	+225.7	+202.8	+143.5					

* Exclusive of cases 2 and 6 (see text)

been stated by Lintzel⁹ that the retention of such large amounts of iron is pathologic and occurs only because the duodenal mucosa has been damaged, but if this were true, surely the absorption of 106.8 mg. from a single dose of 168.6 mg. of iron could not have occurred.

Utilization—The anemia in all cases responded well to the administration of iron and ammonium citrates, and there was a gradual, although irregular, increase in the hemoglobin content of the blood. The usual reticulocyte response was obtained. Heath¹ has shown that the normal response of the hemoglobin to the administration of iron when the initial hemoglobin level is below 7.8 Gm. per hundred cubic centimeters is an increase of 0.16 Gm. per day. An increase of this amount was obtained at times in certain patients, but in no instance did the average for an entire experimental period equal this figure (column

⁹ Lintzel W. Neuere Ergebnisse der Erforschung des Eisenstoffwechsels. Ergebn. d. Physiol. **31**: 844, 1931.

5, table 6) The amount of iron which was administered (iron and ammonium citrate, 15 grains [1 Gm] three times a day, giving approximately 500 mg of metallic iron per day) was only half the dose regularly employed in clinical work and may be considered as sub-optimal if judged by the results obtained by Heath Table 5 gives the average daily response of the hemoglobin for all patients, together with the average daily retention of iron In the fourth period the response of the hemoglobin was the greatest, and it closely approximated the expected increase It is to be noted that there was no correlation between the amount of iron retained and the increase in the hemoglobin content A summary of the iron balances, the increase in the hemoglobin

TABLE 5—*Average Daily Iron Balance and Increase in Hemoglobin Content*

	Control Period	Period 1	Period 2	Period 3	Period 4
Number of patients	8	10	9	6	5
Average daily iron balance, mg	-48	+217.9	+225.7	+202.8	+143.5
Average daily increase in hemoglobin value, Gm per 100 Cc		0.038	0.111	0.056	0.157

TABLE 6—*Data on Retained Iron Utilized as Hemoglobin*

Pa- tients	Average Daily Iron Balance, Mg	Total Intake of Iron, Gm	Total Iron Retained, Gm	Original Hemo- globin, Gm per 100 Cc	Average Daily Hemo- globin, Gm per 100 Cc	Total Hemo- globin Gm	Iron		Retained Iron Utilized as Hemo- globin, %
							Re- tained, %	Used as Hemo- globin, %	
1	140.8	24.773	6.760	4.34	0.1130	272.00	27.8	3.20	11.80
2	189.0	12.436	4.535	1.55	0.0416	50.00	36.4	1.20	3.30
3	225.2	6.189	2.702	7.68	0.1170	70.50	43.6	3.41	7.82
5	151.0	11.456	3.624	5.68	0.0920	111.00	31.6	2.90	9.20
6	72.6	9.276	1.305	5.56	0.0950	85.60	14.0	2.77	19.70
8	266.9	6.231	3.203	6.01	0.0560	33.75	51.4	1.62	3.16
9	368.9	12.411	8.854	6.17	0.0370	45.25	71.3	1.09	1.53
10	261.2	12.392	6.268	4.62	0.1170	141.50	50.5	3.42	6.77

content and the utilization of iron is given in table 6 Since patients 4 and 7 were under observation for only one six day period of administration of iron, a period too short to be of significance as far as the formation of hemoglobin is concerned, they were omitted from this table In calculating the iron utilized in the formation of hemoglobin we have assumed, as did Heath,¹ that the blood volume in each instance was 5 liters Although this is only an approximation, it is sufficiently accurate so that the percentage of utilization based on this figure is of significance It is unfortunate that determinations of the blood volume were not made for all the patients The total increase of the hemoglobin content in 5 liters of blood was determined from the hemoglobin gained per hundred cubic centimeters The iron content of this hemoglobin

was designated as the iron utilized in the formation of hemoglobin. From this was calculated the percentage of the administered iron and of the retained iron which was so utilized.

The percentage of iron retained by the body varied from 14 to 71.3 per cent of that administered by mouth. This was highest in the cases of idiopathic hypochromic anemia (cases 8 to 10), but the difference between the lowest retention in this group and the highest retention in the others was so slight that its significance is doubtful. The average retention for the entire group was 32.6 per cent.

The percentage of administered iron that was utilized in the formation of hemoglobin varied from 1.2 to 3.42, with an average of 1.96 per cent. This is definitely lower than the average of 3.4 per cent found by Heath. The percentage of retained iron that was utilized as hemoglobin varied from 1.53 to 19.7, with an average of 6.32 per cent. This indicates that by far the largest part of the iron which is retained within the body is deposited in some form other than hemoglobin in the blood.

There was no correlation between the original hemoglobin level and the amount of iron retained or the percentage utilized, and the type of anemia had no bearing on these results.

The average daily nitrogen balance for all patients during the control periods was plus 0.18 Gm., and with the administration of iron it increased to plus 1.32 Gm. per day. The phosphorus balance increased from plus 0.07 Gm. in the control periods to plus 0.19 Gm. during the administration of iron. This is not in accord with the results of animal experimentation, which suggest that the daily administration of iron leads to a decrease in the phosphorus content of the blood.¹⁰

The total leukocyte and differential counts showed no significant changes during iron therapy.

COMMENT

A summary of the present concept of iron metabolism is as follows. Absorption of iron administered by mouth takes place throughout the entire gastro-intestinal tract but occurs mainly in the duodenum and in the upper portion of the small intestine.¹¹ The iron is eliminated almost entirely through the gastro-intestinal tract, chiefly through the colon. The processes of elimination and absorption are reversible and

10 Brock, J. F., and Diamond, L. K. Rickets in Rats by Iron Feeding, *J. Pediat.* **4**: 442 (April) 1934.

11 (a) Robschey-Robbins, F. S. The Regeneration of Hemoglobin and Erythrocytes, *Physiol. Rev.* **9**: 666 (Oct.) 1929. (b) M'Gowan, J. P. The Absorption and Excretion of Iron by the Intestines and the Nutritional and Therapeutic Value of Its Salts, *Edinburgh M. J.* **37**: 85 (Feb.) 1930.

may occur at the same location¹² Small amounts are eliminated in the urine and bile, but even parenterally administered iron is excreted almost entirely through the intestinal tract⁹ The absorbed iron is transmitted mainly, if not entirely, by the blood stream, although the form in which it is transported is unknown¹³ It has been shown, however, that the oral administration of iron in large doses does not appreciably increase the iron content of the blood plasma outside the portal circulation¹⁴ It may be accepted from animal experimentation that the liver is the principal storehouse for iron¹⁵ Smaller amounts are stored in other parts of the reticulo-endothelial system, and aside from the liver, the spleen is the most important storage depot The iron content of the liver may be increased by the administration of iron to eight times its normal value and that of the spleen to four times its normal value^{11a} There is no decrease in the iron content of muscle (muscle hemoglobin and parenchymal iron) with long continued anemia, nor is this value increased with the administration of large amounts of the metal³

Our observations have established the fact that large amounts of iron are retained in the body as a result of the oral administration of iron and ammonium citrates, and from the aforementioned results of animal experimentation it seems logical to conclude that this iron is retained primarily in the liver and spleen If our present ideas concerning the total iron content of the body are correct (blood hemoglobin, muscle hemoglobin and parenchymal or respiratory iron of the cells), it must be admitted that all the 676 Gm retained in case 1 and the 885 Gm retained in case 9 could not be put to a useful purpose immediately when such a small percentage was utilized in the formation of hemoglobin The storage capacity of the liver and its efficiency in removing iron from the portal circulation must be great, since the amount of iron in the plasma of the general circulation is not elevated appreciably When one realizes the amount of iron retained and its probable storage in the liver, it must cause some concern over the possibility of the development of pigmentary cirrhosis of this organ similar to that which occurs in hemochromatosis Although we are not aware that any case of this type has been reported, the possibility seems real in those cases in which iron is administered over a long period

12 Verzar, F, in Bethe, A, von Bergmann, G, Embden, G, and Ellinger, A *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1929, vol 4, p 72 M'Gowan^{11b}

13 Lintzel⁹ Robscheit-Robbins^{11a}

14 Marlow, A, and Taylor, F H L Constancy of Iron in the Blood Plasma and Urine in Health and in Anemia, *Arch Int Med* **53** 551 (April) 1934

15 Polson, C J The Storage of Iron Following Its Oral and Subcutaneous Administration, *Quart J Med* **23** 77 (Oct) 1929 Lintzel⁹ Robscheit-Robbins^{11a}

Lintzel¹⁰ stated the belief that the retention of such large amounts of iron is pathologic. He said that the body finds a rate of excretion of iron which agrees with the intake, so that it is soon in balance, and when 100 or 200 mg. of iron is given its excretion is prompt. Our results indicate that large amounts are retained by the body, and the retention of 63 per cent of a single dose of iron in case 6 does not bear out Lintzel's supposition that the iron first damages the mucosa before being absorbed.

The intermediary steps in iron metabolism are unknown, but it has been suggested that idiopathic hypochromic anemia may be due to a faulty internal metabolism of iron. This hypothesis is not borne out by these experiments, since the patients with an idiopathic form of anemia (patients 8 to 10) retained iron as well as, if not better than, the others and also showed a percentage utilization in hemoglobin formation which was equal to the utilization by those with chronic hemorrhage.

It must be admitted that our conclusions as to the utilization of iron in the formation of hemoglobin are approximations, since determinations of the blood volume are lacking. The results are somewhat lower than those obtained by Heath,¹ even though we were giving a smaller amount of iron, which should have resulted in a higher percentage of utilization. More significant is the percentage of the retained iron that goes to form hemoglobin, indicating that a large part of the iron that is retained is held in storage rather than being utilized immediately. This is in keeping with the experimental work of Whipple,¹⁶ who found that the optimum dose of iron for dogs rendered anemic by repeated loss of blood exceeded by threefold the iron removed in the hemoglobin. He concluded that the iron had some effect on the body aside from the replacement of hemoglobin.

It has been shown by Heath² that 96 per cent of the iron administered to patients parenterally is utilized in the formation of hemoglobin, and similar results were obtained by Whipple¹⁷ in animal experiments. Whipple reasoned by analogy that, since iron administered intravenously is utilized quantitatively in the formation of hemoglobin, the amount of iron absorbed from the gastro-intestinal tract after oral administration may be estimated from the amount of new-formed hemoglobin. This assumption is not verified by our experiments on human beings, which showed that only a small percentage of the retained iron is so utilized.

16 Whipple, G. H., and Robschert-Robbins, F. S. Blood Regeneration in Severe Anemia. Optimum Iron Therapy and Salt Effect, *Am J Physiol* **92** 362 (March) 1930.

17 Whipple, G. H., and Robschert-Robbins, F. S. Iron and Its Utilization in Experimental Anemia, *Am J M Sc* **191** 11 (Jan.) 1936.

Where the remainder of this is stored can only be surmised, but it seems probable that it remains in the liver, the spleen and the reticulo-endothelial system

SUMMARY

With the oral administration of iron and ammonium citrates to patients with hypochromic anemia large amounts of iron are retained by the body

An average of 32.6 per cent of the iron administered was retained by the body

Approximately 1.96 per cent of the iron administered was utilized in the formation of hemoglobin

There was no correlation between the amount of iron retained and the increase in the hemoglobin content

CHRONIC NEPHRITIS IN RATS FED HIGH PROTEIN DIETS

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The metabolism of carbohydrate and fat results in almost complete oxidation or storage of these substances in the body. In contrast, the metabolism of protein leads to the formation of several end-products that are eliminated by the kidney, and the excretion of these products entails work by the kidney. The possibility that this work or some specific product or products may eventually lead to pathologic changes in this organ has been the incentive for much study. The results obtained by feeding animals, chiefly rabbits and rats, diets high in protein have been conflicting. Many of the early investigations are open to the criticism that the necessary food accessories were missing from the diet. The use of rabbits for this type of study is questionable, unless the effects of vegetable proteins are being determined. That in these animals spontaneous nephritis is prone to develop is, in any case, disturbing. The nutritive requirements of the rat are better understood, and it is known to thrive on diets containing animal proteins. But even with rats, the results obtained by different investigators have been at variance. Possibly differences in diets which appear to be slight may account for some of these discordances. The best positive results have been obtained by Newburgh and Curtis,¹ who found that diets containing large quantities of beef liver produce severe renal damage. Diets containing large quantities of beef muscle also were found to be injurious, while casein proved to be relatively harmless. No useful purpose would be gained by considering at length the many other experiments reported in the

From the Biochemical Laboratory and the Hegeman Memorial Laboratory of the Metropolitan Life Insurance Company

1 Newburgh, L H, and Curtis, A C. Production of Renal Injury in the White Rat by the Protein of the Diet, Arch Int Med **42** 801 (Dec) 1928

literature The reader who is interested in the details is referred to the excellent reviews by Bischoff² and Mitchell³

The conflicting results just mentioned led us to undertake the experiments recorded in this paper, in the hope that by giving special attention to the care of the rats and to the composition of their diets we might obtain more uniform and reliable results, which would be useful in explaining certain phenomena of nephritis A preliminary report of some of our first experiments appeared in 1931⁴

PLAN OF EXPERIMENTS AND METHODS

The albino rats used were bred in our laboratory from stock obtained originally from the Wistar Institute Within a few days after weaning they were placed on the experimental diets They were kept in individual cages of the Yale type, which were changed and sterilized twice weekly A fresh blotter for the bottom of each cage pan was supplied daily, except Sundays Food and water were always available, while supplements of carrots and lettuce were fed twice weekly Accurate records were kept of the body weight and consumption of food Since February 1933 the animals have been housed under favorable surroundings in an air-conditioned room maintained constantly at a temperature of 23 or 24 C

Specimens of urine were collected by placing the rats overnight in metabolism cages without food Samples were obtained monthly, beginning one month after starting the experiment The entire sediment from each specimen was examined for all formed elements Albumin was estimated quantitatively by the sulfo-salicylic acid method

The rats were allowed to live until it was evident that death would soon occur They were then anesthetized with sodium amytal, and samples of blood were removed from the heart for chemical analysis The urea, nonprotein nitrogen, albumin, globulin and cholesterol contents of the blood and plasma were determined by conventional methods The kidneys and other organs, after their gross appearance had been noted, were removed, measured, weighed and transferred to a dilute solution of formaldehyde U S P (1:10) or to Zenker's solution for subsequent histologic examination

The term nephrectomy is used in this paper to mean the removal of the right kidney This operation was performed with the animal under anesthesia induced by sodium amytal That the young rats stood this operation well is indicated by their desire to eat soon after the effect of the anesthetic disappeared and by an operative mortality of less than 1 per cent

Since the beginning of this study in 1929 the experimental work has all been carried on in the biochemical laboratory of the Metropolitan Life Insurance Company in New York city, the histologic examinations have been made at the Hege-man Memorial Laboratory in Mt McGregor, N Y Throughout the study the

² Bischoff, F The Influence of Diet on Renal and Blood Vessel Changes, *J Nutrition* **5** 431, 1932

³ Mitchell, H H The Physiological Effects of Protein, *J Nutrition* **1** 271, 1929

⁴ Blatherwick, N R, Medlar, E M, Connolly, J M, and Bradshaw, P J Nephritis in Unilaterally Nephrectomized White Rats Living upon High Protein Diets, *J Biol Chem* **92** 1331, 1931

only data submitted to the pathologist were the number of the rat and the number of the diet on which it was fed. The results of his histologic examinations were not revealed to the workers in the city of New York until late in the course of the work, after the organs of more than 800 rats had been examined. The total number of rats used exceeded 1,000. The data here presented represent the most significant findings of our study.

PATHOLOGIC EFFECTS OBTAINED WITH DIFFERENT DIETS

A good criterion of whether the diet can produce chronic nephritis is evidence of histologic change in the renal structure. In the pathologic analyses to be presented here the following terms are used to indicate the extent of renal involvement.

Normal There is no evidence of abnormality in the section of kidney.

1 plus The glomeruli and the tubular epithelium appear normal. There may be a few small collections of lymphocytes or an occasional tubular cast. Such kidneys do not represent a true condition of nephritis, but they are not entirely normal.

2 plus Sclerosing glomeruli, abnormal tubular epithelium, tubular casts and collections of lymphocytes may all be present. Less than one fourth of the section is abnormal.

3 plus The same as 2 plus except that more than one fourth and not over two thirds of the tissue is involved. Fibrosis is usually present.

4 plus The same as 2 plus except that two thirds or more of the tissue is involved. Fibrosis is always present and may be marked.

In most instances histologic examination was made of the heart, liver, spleen, adrenal glands and aorta in addition to the kidney of each animal. Abnormal conditions were frequently noted in organs other than the kidney, especially calcification of the aorta, but at present it is not possible to correlate all these changes directly and consistently with the renal pathologic picture. Consequently, we have presented in the accompanying tables the data relative to the kidney and aorta only.

Table 1 gives a general summary of the data for 418 rats. The rats are divided as to sex and as to whether nephrectomy had been performed. It will be noted that in the nephrectomized rats nephritis developed much more frequently than in the animals with both kidneys. It is evident, also, that severe nephritis occurred more frequently in males than in females. This difference between the sexes was especially marked in the non-nephrectomized animals. Death occurred earlier in the male rats, the shortest period of survival being among the nephrectomized males.

The combined data for all the diets fed are given in table 1 and the data for each individual diet are analyzed in tables 2 to 7. In table 2 are the results for the rats fed stock diet 2, which has the following composition:

Stock Diet 2	Percentage
Wheat	55
Milk	25
Beef muscle	12
Yeast A	5
Sodium chloride	2
Calcium carbonate	1

The milk and yeast in this and subsequent diets are dry. (Several brands of yeast were employed in the various diets, and information in this regard will be furnished on request.) Lean beef muscle is carefully freed of fat and connective tissue, passed through a chopper, dried at a moderate temperature and then pulverized.

TABLE 1—*Summary of the Data for All the Rats*

Sex	Num ber of Rats	Ne phrec tomy	Average Length of Life, Days	Nephritis						Aorta		
				0	1+	2+	3+	4+	3+ or 4+, %	Num ber Exam ined	Num ber Cal cified	Calci fied, %
M	65	Yes	430	2	2	5	9	47	86.1	24	10	41.7
M	122	No	515	5	26	17	16	10	21.3	119	4	3.3
F	92	Yes	512	9	7	11	25	40	70.6	42	1	16.6
F	139	No	516	74	40	16	6	3	6.4	123	0	0.0
Total or av erage	418		504	138	75	49	56	100	37.3	308	21	6.5

TABLE 2—*Summary of the Data for the Rats Fed Stock Diet 2*

Sex	Num ber of Rats	Ne phrec tomy	Average Length of Life, Days	Nephritis						Aorta		
				0	1+	2+	3+	4+	3+ or 4+, %	Num ber Exam ined	Num ber Cal cified	Calci fied, %
M	3	Yes	531	2	1							
M	16	No	574	10	6					9		
F	5	Yes	612	4		1						
F	27	No	536	24	2	1				9		
Total or av erage	51		549	40	9	2				18		

Here it is evident that neither severe nephritis nor calcification of the aorta developed. As all the aortas appeared normal on gross examination, only eighteen were examined histologically. The shortening of the average period of survival of the non-nephrectomized female rats was apparent rather than real, for the reason that these rats were taken from the breeding stock and were killed after they had become unsatisfactory for breeding purposes.

Table 3 gives the findings for the rats fed liver diet 1, the composition of which is as follows

Liver Diet 1	Percentage
Liver	75
Lard	16
Yeast A	5
Cod liver oil	3
Salt mixture	1

Beef liver is carefully freed of its connective tissue and vessels, cut into small pieces, dried at a moderate temperature, passed through a chopper, dried again at a moderate temperature and then pulverized. This diet is the one used by Newburgh and Curtis¹. The salt mixture used in this and other diets is that of Osborne and Mendel⁵.

TABLE 3—Summary of the Data for the Rats Fed Liver Diet 1

Sex	Number of Rats	Nephrectomy	Average Length of Life, Days	Nephritis						Aorta		
				0	1+	2+	3+	4+	3+ or 4+, %	Number Examined	Number Calcified	Calcified, %
M	9	Yes	402					9	100.0			
M	17	No	547		2		6	9	88.2	16	2	12.5
F	4	Yes	487			1	1	2	75.0			
F	10	No	538	1	4		3	2	50.0	10		
Total or average	40		506	1	6	1	10	22	80.0	26	2	7.7

Marked involvement of the kidney had a high incidence in all groups of animals fed this diet, with the nephrectomized animals showing a greater proportion of marked nephritis than the non-nephrectomized animals. It was noticeable that abnormality of the kidneys occurred much more frequently among the rats fed this liver diet than among the controls on stock diet 2 (97.5 per cent as contrasted with 20 per cent).

Calcification of the aorta was noted occasionally in the animals fed liver diet 1. The survival period of the nephrectomized animals was shorter than that of the rats with both kidneys. Severe nephritis was somewhat less frequent in the females than in the males.

In table 4 are given the data for the rats fed liver diet 12. The composition of this diet is as follows:

Liver Diet 12	Percentage
Liver	30
Corn starch	43
Lard	15
Yeast A	5
Cod liver oil	3
Salt mixture	4

⁵ Osborne, T. B. and Mendel, L. B. The Nutritive Value of the Wheat Kernel and Its Milling Products, J. Biol. Chem. **37**: 557, 1919.

In the nephrectomized rats in this group marked nephritis developed frequently but less so than when liver diet 1 was used. This difference between the effects of the two diets was greater in the case of the intact rats. Again the males showed nephritis more often than the females. The high incidence of aortic calcification in the nephrectomized males is inconsistent with the observations on rats fed liver diet 1, unless factors other than the dietary factors were concerned.

TABLE 4—*Summary of the Data for the Rats Fed Liver Diet 12*

Sex	Number of Rats	Nephrectomy	Average Length of Life, Days	Nephritis						Aorta		
				0	1+	2+	3+	4+	3+ or 4+, %	Number Examined	Number Calcified	Calcified, %
M	5	No	326	3	1		1		20.0	5		
M	13	Yes	421		1	1	2	9	84.6	9	5	55.5
F	6	No	520	4	1	1				6		
F	10	Yes	505	1	3	1	5		50.0	7		
Total or average	34		449	8	6	3	8	9	50.0	27	5	18.5

Attempts were then made to find a diet on which the females also would consistently show severe nephritis. Accordingly desiccated thyroid was added to the diet to stimulate metabolism. The results of this experiment are given in table 5. The composition of the diets used follows:

Liver Diet 14	Percentage
Liver	75.0
Lard	15.0
Yeast A	5.0
Cod liver oil	3.0
Salt mixture	1.0
Calcium carbonate	0.6
Thyroid, desiccated	0.4

Liver diet 15 is the same as liver diet 14, except that calcium carbonate is increased to 0.8 per cent and thyroid is decreased to 0.2 per cent.

Liver diet 20 is the same as liver diet 14, except that calcium carbonate is increased to 0.9 per cent and thyroid is decreased to 0.1 per cent.

Only nephrectomized females were used. All showed marked renal lesions, with the exception of 1 rat fed liver diet 15, which died after one hundred and fifty-three days. It is interesting that the average survival period in the three groups increased progressively as the quantity of thyroid was lessened (being one hundred and forty-eight days with 0.4 per cent thyroid and five hundred and thirty-nine days with 0.1 per cent). The consistent appearance of calcification of the aorta in animals fed these diets is to be noted also.

Since liver diets so frequently produced nephritis, it was necessary to determine whether nonliver diets also cause this condition. Accordingly the following diets were used:

Casein Diet 1	Percentage
Casein	75
Lard	16
Yeast A	5
Cod liver oil	3
Salt mixture	1

This diet is the same as that used by Newburgh and Curtis.¹

Casein diet 2 differs in that 37.5 parts of dried milk is substituted for an equal amount of casein in casein diet 1.

Diet 2899	Percentage
Wheat	30.0
Casein	20.0
Corn, yellow	17.0
Peas, green split	15.0
Beans, navy	12.5
Cod liver oil	3.0
Calcium carbonate	1.5
Sodium chloride	1.0

This diet is the one used by Polvogt, McCollum and Simmonds,⁶ who found that it induces nephritis in rats.

Diet 2899, modified, is made by mixing corn, peas and beans and allowing them to stand overnight in water. They are next cooked in an autoclave at a temperature of 120 C for two and one-half or three hours and then dried, pulverized and mixed with the other ingredients of diet 2899.

Diet 2899 A	Percentage
Wheat	30.0
Liver	20.0
Corn, yellow	17.0
Peas, green split	15.0
Beans, navy	12.5
Cod liver oil	3.0
Calcium carbonate	1.5
Sodium chloride	1.0

Diet 2899 A, modified, is made by treating corn, peas and beans as for diet 2899, modified. They are then mixed with the other ingredients of diet 2899 A.

The results obtained with these diets are given in table 6. It will be noted that nephritis did develop in animals on a casein diet, provided it was fed for a sufficient length of time. Reduction of the quantity of casein led to less frequent nephritis. Diet 2899, however,

6 Polvogt, L. M., McCollum, E. V., and Simmonds, N. Production of Kidney Lesions in Rats by Diets Defective Only in That They Contained Excessive Amounts of Protein, *Bull. Johns Hopkins Hosp.* **34**: 168, 1923.

whether raw or cooked, failed to induce nephritis. When this diet was fed uncooked, skeletal bone deformities and overgrowth of the incisor teeth occurred. The overgrowth was at times so great that the upper incisors curled backward and upward and, occasionally, pierced the brain cavity. However, when the diet was cooked abnormalities of the bones and teeth failed to develop. From a nutritional standpoint this diet, whether raw or cooked, was not satisfactory for rats kept under our conditions.

TABLE 5—*Summary of the Data for the Nephrectomized Female Rats Fed Liver Diets Containing Thyroid*

Liver Diet	Thyroid, %	Sex	Num-ber of Rats	Average Length of Life, Days	Nephritis					3+ or 4+, %	Aorta		
					0	1+	2+	3+	4+		Num-ber Examined	Num-ber Calcified	Calcified, %
14	0.4	F	3	148					3	100.0	3	1	33.3
15	0.2	F	6	276	1			1	4	83.3	5	1	20.0
20	0.1	F	9	539				3	6	100.0	8	2	25.0
Total or average			18	386	1			4	13	94.4	16	4	25.0

TABLE 6—*Summary of the Data for the Rats Fed Other Than Liver Diets*

Diet	Sex	Rats	Average Length of Life, Days	Nephritis					3+ or 4+, %	Aorta		
				0	1+	2+	3+	4+		Num-ber Examined	Num-ber Calcified	Calcified, %
Casein 1	M	6	676	1	1	2	2		33.3	6		
Casein 1	F	4	722		1	2	1		25.0	4		
Casein 2	M	6	694		1	4		1	16.6	6		
Casein 2	F	6	631	3	1	2				6		
2899 and 2899 A	M	17	546	17						17		
2899 and 2899 A	F	15	518	15						15		
2899 modified and 2899 A modified	M	11	588	11						11		
2899 modified and 2899 A modified	F	11	625	11						11		
Total or average		76	596	58	4	10	3	1	5.26	76		

Early in our experimental work we thought it desirable to increase the vitamin content in the rations, therefore, in stock diet 2 we substituted 5 per cent of irradiated yeast B for an equivalent quantity of yeast A. After this change abnormal renal conditions began to appear unexpectedly in the control animals. This led to a comparative study of the effects of irradiated and nonirradiated yeast B, using the following diets:

Yeast diet 1 is the same as stock diet 2 except that an equivalent quantity of irradiated yeast B is substituted for yeast A.

Yeast diet 2 differs from stock diet 2 in that an equal quantity of nonirradiated yeast B is substituted for yeast A.

TABLE 7—Summary of the Data for the Rats Fed Yeast Diets

Yeast Diet	Sex	Number of Rats	Nephrectomy	Average Length of Life, Days	Nephritis				Aorta		Hydro-nephrosis		Calcification of Kidney		Renal Calculi	
					0	1+	2+	3+	4+	3+ or 4+, %	Number Examined	Number Calcified, %	Cases	%	Cases	%
1	M	3	Yes	270			1	2		66.7	3	100.0	2	66.7	3	100
1	M	6	No	359	6					0	6	33.3	5	83.3	6	100
1	F	3	Yes	203			1	2		66.7	3	33.3	1	33.3	3	100
1	F	12	No	497	4	2	5	1		8.3	12	—	7	58.3	12	100
Total or average		24		410	10	2	7	5		20.8	24	25.0	9	37.5	24	100
2	M	4	Yes	360				1	3	100.0	4					
2	M	4	No	503	2	1		1		25.0	3					
2	F	3	Yes	183		1	1		1	33.3	2					
2	F	7	No	637	4	1	1	1		14.3	7		1	14.3		
Total or average		18		521	6	3	2	3	4	33.3	16	—	1	5.5		

The results obtained with these diets are given in table 7. It will be noted that nephritis occurred with both diets, especially in the nephrectomized rats. In the intact rats fed irradiated yeast, calcification of the aorta, hydronephrosis, calcium deposits in the renal tissue, renal calculi and crystals of dicalcium hydrogen phosphate in the urine were consistently observed, such abnormalities were absent when non-irradiated yeast was used. These results emphasize the importance of seemingly minor factors in experiments dealing with dietary effects.

STUDY OF THE PATHOGENESIS OF NEPHRITIS

Having found that such extensive alterations in the structure of the kidney followed consistently when rats were fed certain diets, we proceeded to study the pathogenesis of these changes. Groups of nephrectomized animals were given diets known to produce nephritis, and the nephrectomized control animals were fed the innocuous stock diet 2. The animals were then killed at intervals in an attempt to demonstrate the site of the initial lesion in the kidney. The results are given in table 8. The data for the fatty infiltration of the liver also are given to show that this condition occurs commonly in rats fed liver diets. We have found that one substance responsible for this effect is the cholesterol contained in liver.⁷ It should be noted that a considerable increase in the amount of hepatic fat, detectable by chemical analysis, may occur without its presence being shown by histologic examination. This fatty infiltration is not present consistently in rats in which nephritis is developing. However, its presence may indicate that the factors producing the renal changes are acting on other organs. Liver diets 1 and 3 were used in this study. The composition of the latter follows:

Liver Diet 3	Percentage
Liver	72
Lard	15
Yeast A	5
Cod liver oil	3
Sodium bicarbonate	3
Calcium carbonate	1
Salt mixture	1

This quantity of sodium bicarbonate in the diet was found to produce a neutral or slightly alkaline urine when fed to rats.

⁷ Blatherwick, N. R., Medlar, E. M., Bradshaw, P. J., Post, A. L., and Sawyer, S. D. The Dietary Production of Fatty Livers in Rats. *J. Biol. Chem.* **103**: 93, 1933.

The results of this study show that of the 38 rats on stock diet 2 32 had normal kidneys, 4 had slight alterations in no way suggestive of nephritis and 2 had marked nephritis. The occurrence of nephritis in these 2 animals is at variance with the rest of the data for this diet and is difficult to explain but may have been due to the presence of irradiated yeast in the diet at the time the two animals received it.

The kidneys of the rats fed the liver diets gave a different picture from that of the ones on the stock diet. Among the rats fed liver,

TABLE 8—*A Study of the Pathogenesis of Nephritis*

	No of Rats	Days on Diet	Fatty Infiltration of Liver			Nephritis				
			0	Slight	Mild to Moderate	0	1+	2+	3+	4+
Stock diet 2	4	63	4			4				
	3	106	3			3				
	3	127	3			2	1			
	3	134	3			3				
	3	162	3			2	1			
	3	173	3			3				
	3	190	2	1		2	1			
	3	215	3			3				
	3	225		3		2	1			
	3	256	3			1				2
	2	291	2			2				
	4	333	4			4				
	1	372	1			1				
Total or average	38		34	4	—	32	4	—	—	2
Liver diet*	4	59	4			4				
	3	59	3			2	1			
	3	89		1	2	1	2			
	3	105		3			3			
	3	121			3		3			
	3	145		3			3			
	3	151		2	1	1		2		
	3	180		1	2		2	1		
	3	190	3					1	1	1
	2	212			2		1	1		
	3	228	3				1	1		1
	2	270	2				1	1		
Total or average	35		15	10	10	8	17	7	1	2

* In this part of the table liver diets 1 and 3 are not designated, since other experiments showed that both were effective in producing nephritis. Although the presence of sodium bicarbonate and calcium carbonate in liver diet 3 rendered the urine neutral or slightly alkaline, the development of nephritis was not retarded.

only 8 had normal kidneys, 17 showed abnormalities not suggestive of nephritis, 7 showed mild, 1 moderate and 2 severe nephritis. Prior to one hundred and fifty days there was no evidence to suggest that general nephritis would eventually develop, after that time the results were not sufficiently uniform to fix the site of the initial lesion in the kidney. From the evidence we conclude that the functional derangement of the kidney antedates considerably the appearance of the histologic changes characteristic of nephritis, but once the latter changes begin frank and severe nephritis develops quickly.

THE HISTOLOGIC PICTURE OF THE NEPHRITIC KIDNEY

The essential changes in the kidney occur in the glomeruli and tubules. The glomerular changes begin as focal hyalinization in the capillary tuft and end in complete obliteration of the capsular space. Inflammation is never marked, but when present it is shown by the infiltration of monocytes and an occasional lymphocyte. The capillary tuft commonly contains demonstrable fat, which is scattered throughout the structure either in small isolated foci or in considerable quantities. The origin of this fat is obscure, but there is a suggestion that it may come from the circulating blood and may be embolic. The number of glomerular units involved varies with the extent of the nephritis—from a few in cases of mild nephritis to many in cases of severe nephritis. In the latter cases the glomeruli show varying degrees of fibrosis, with some units apparently uninvolved and retaining their normal structure. Evidently the number of functional glomeruli becomes greatly decreased as the disease progresses.

The changes in the tubular epithelium appear to be limited in the early stages at least, to the distal portion of the tubule. In this region the earliest changes observed are the presence of demonstrable fat and, with certain diets, especially liver 1, a considerable quantity of pigment the nature of which is not understood. This pigment does not contain iron and in some instances stains faintly with sudan III stain. It is not a constant feature, as some of the kidneys in which severe nephritis was present contained practically none. Constant features are the enlargement of the epithelial cells of the distal tubule and their staining a more intense blue than in the normal kidney. The latter change is not observed in the proximal tubules, for there the cytoplasm retains its pink-staining characteristics. Evidently, hyperplasia of the epithelium of the distal tubules occurs frequently. Mitotic figures may be present at certain stages, and often the entire lumen of the distal portion of the tubule is enlarged and filled with well preserved epithelial cells. At a later stage there is disintegration of the epithelial cells, always accompanied with infiltration of lymphocytes, which may be marked. Fibrosis occurs concurrently with or following these changes, and the final histologic picture is that of scar tissue formation without tubular epithelium and with little lymphocytic infiltration.

As hyperplasia, disintegration of the distal tubular epithelium and fibrosis occur, there appears to develop a damming back of the urinary secretion into the proximal convoluted tubules. This leads to dilatation of the tubules, with the formation first of granular debris and later of hyaline casts. The end-result is cystic dilatation of the tubules, within which are large numbers of casts, some containing demonstrable fat. There is little evidence of hyperplasia of the epithelium in the proximal

convoluted tubules, which in instances of marked distention may be completely disintegrated. The epithelial cells may or may not contain fat or pigment.

There appear to be no consistent and significant changes in the walls of the arteries in these kidneys, that is, the development of nephritis seems to be unrelated to vascular changes, exclusive of those which may occur in the glomerular tuft.

It may be interesting to consider the significance of calcification of the aorta as encountered in our experimental rats. The histologic picture shows calcium, either in plaques or in diffuse deposits, in the median portion of the artery. Otherwise, the artery appears normal. No evidence of an inflammatory reaction and no semblance of the process of arteriosclerosis, as seen in man, were noted. We have encountered 21 instances of calcification of the aorta, 6 cases were in a group of 24 rats on a diet which contained 5 per cent irradiated yeast, 4 cases occurred in a group of 18 rats fed a liver diet containing thyroid and the 11 remaining cases were found at random in groups of animals on other liver diets. Dietary factors possibly bear directly on calcification of the aorta, as this condition has not been observed in the examination of several hundred of our rats on nonnephritis-producing diets. Just what these factors are and how they induce calcification is not understood. An examination of the data on the blood indicates clearly that hypercholesteremia was no more frequent in the rats with calcification of the aorta than in those without it.

Our interpretation of the pathologic processes described is as follows. The glomerular changes are probably dependent on an alteration in the constituents of the blood. This produces a change in the filter apparatus, eventuating in complete obliteration of the functional glomerulus by fibrosis. The altered filtration allows passage into the urine of substances which profoundly affect the epithelium of the distal renal tubule. Hyperplasia and later disintegration of these cells then occur and are followed by lymphocytic infiltration and fibrosis. A damming back of urinary secretion results. The final picture (fig 1) resembles that seen in man in so-called chronic atherosclerotic nephritis, but without the presence of atherosclerosis. We suggest that the whole picture represents a phenomenon due to overwork of the distal portion of the renal tubule resulting from changes in the filtering ability of the glomerular tuft.

URINARY OBSERVATIONS

In man the laboratory recognition of nephritis rests on the presence, quantity and persistence of albumin in the urine, together with the occurrence of casts and red blood cells in the sediment, on evidence in the blood of the retention of nitrogenous substances, and, in certain

conditions, of a lowered albumin-globulin ratio and an increased cholesterol content, and on functional renal tests, such as fixation of the specific gravity, the urea clearance and the ability to excrete phenol-sulfonphthalein. The presence or absence of such phenomena in the

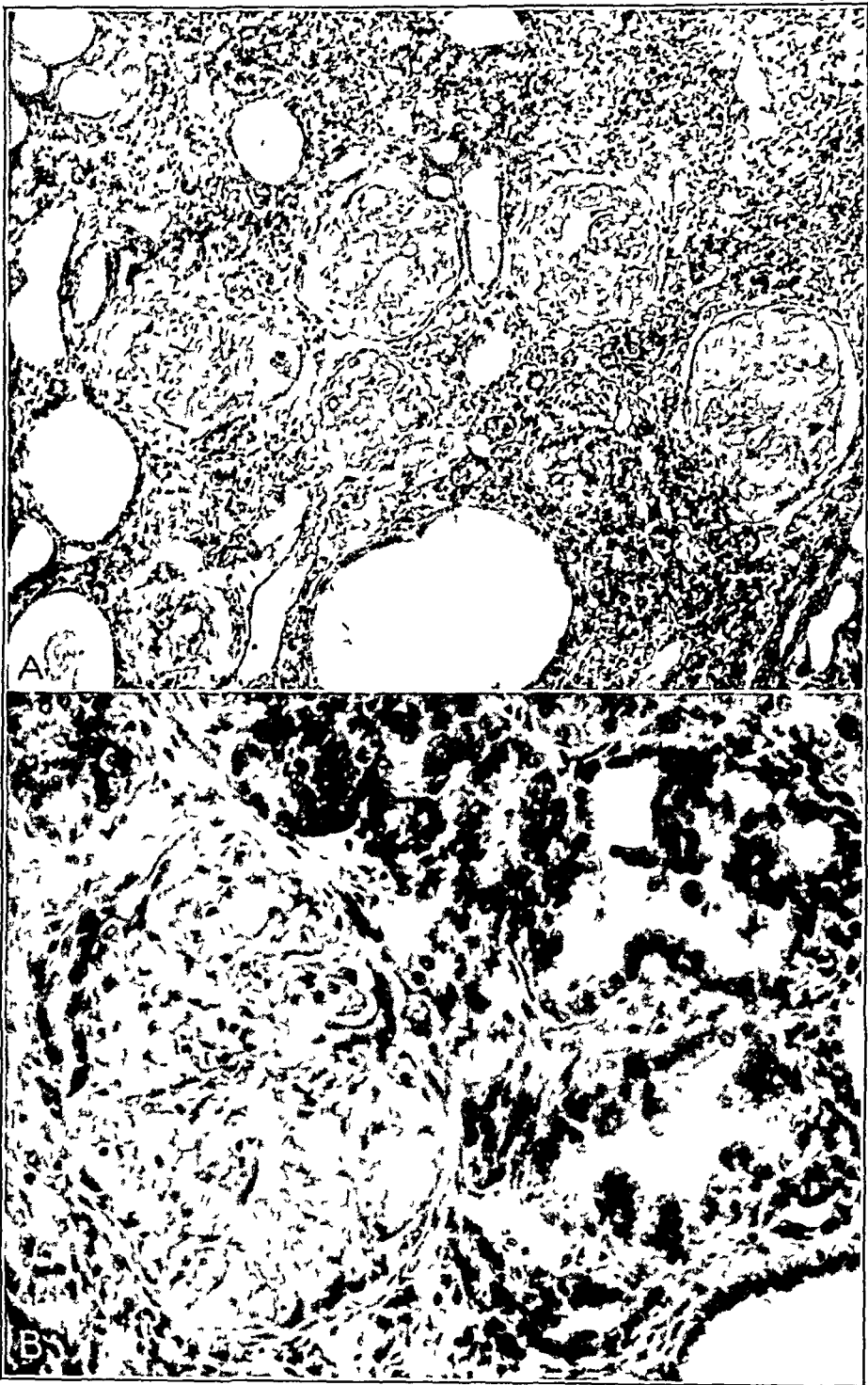


Fig 1—*A*, photomicrograph, $\times 300$, showing the type of nephritis encountered. This is regarded as 4 plus nephritis in our classification. *B*, a photomicrograph of higher power, $\times 600$. Note the sclerosing glomerulus and the hyperplastic epithelium of the distal renal tubule.

that must be determined if one is to learn whether the pathologic process in this animal resembles the manifestations in man. We have accumulated data for the urine relative to the albumin, casts and other formed elements and for the blood relative to the retention of nitrogenous substances, the albumin-globulin ratio and the cholesterol content.

In tabulating the data for the urine and blood the rats have been considered in the following groups: (a) rats without nephrectomy which showed normal kidneys on histologic examination, (b) rats with one kidney removed and with the remaining kidney histologically normal, (c) rats without nephrectomy which had 3 plus or 4 plus nephritis histologically and (d) rats with one kidney removed and with 3 plus

TABLE 9—*Albumin and Casts in the Urine of Intact and Nephrectomized Rats with Normal Kidneys or with 3 + or 4 + Nephritis*

No of Rats	Sex	Nephrectomy	Condition of Kidney at Necropsy	Albumin in Urine			Casts in Urine			
				No of Examinations	Over 0.3 %	Over 0.1 %	Positive, %	No of Examinations	No of Positive Examinations	Positive Examinations, %
20	M	No	Normal	287	24		8.4	291	25	8.6
20	F	No	Normal	280		19	6.8	287	13	4.5
13	M	Yes	Normal	124	67		54.4	126	32	25.0
17	F	Yes	Normal	235		86	36.6	236	92	39.0
20	M	No	3+ or 4+ nephritis	342	268		78.3	327	193	60.0
7	F	No	3+ or 4+ nephritis	115		38	33.3	120	45	37.5
20	M	Yes	3+ or 4+ nephritis	242	199		82.0	244	181	73.8
20	F	Yes	3+ or 4+ nephritis	309		226	70.0	316	229	72.4
5*	M	No	Hydronephrosis	47	0		0.0	48	18	37.5
6*	F	No	Hydronephrosis	86		15	17.4	87	47	54.0
4†	M	No	Normal	45	0		0.0	45	5	11.1
5†	F	No	Normal	89		8	9.0	90	24	26.6

* Irradiated yeast diet
† Nonirradiated yeast diet

or 4 plus nephritis in the remaining organ. We found it advisable to subdivide the groups according to sex as far as the urine was concerned, since the albumin content of the urine is normally greater in the male than in the female, as has been shown by Bell⁸ and Shih⁹. The latter stated his conclusion that most of this excess protein originates in the genital tract. That such may be the case is indicated by the usual presence of large numbers of spermatozoa in the urine of our male rats.

In table 9 are assembled the data for albumin and casts obtained from over 2,000 urinalyses. After careful study of the results of the

8 Bell, M. E. Albuminuria in the Normal Male Rat, *J. Physiol.* **79** 191, 1933

9 Shih, H. E. The Origin of Protein in the Urine of Albino Rats, *Am. J. Physiol.* **113** 120, 1935

examinations of normal rats, we have been led to consider as abnormal an albumin content over 0.3 per cent in the male and over 0.1 per cent in the female rat and the presence of any casts. An increase in the albumin content or the presence of casts in intact rats with histologically normal kidneys did occur but was rare. In nephrectomized rats, with the remaining kidney histologically normal, there occurred a significant increase in the abnormal albumin values and the presence of casts. Rats having moderate or severe nephritis showed a much higher incidence of abnormal albumin values and of casts than did the non-nephritic animals. This is true for both nephrectomized and non-nephrectomized males and females. Rats which showed hydronephrosis on diets containing irradiated yeast showed a marked incidence of casts, with a slight increase in the albumin content, animals on diets containing nonirradiated yeast showed a similar though less marked picture. Male rats showed a higher percentage of abnormal findings than females in all groups except those on the yeast diets, in which the reverse was true.

The data relative to albumin, casts and the albumin-globulin ratio obtained for the rats used in the study of the pathogenesis of nephritis are given in table 10. Here a marked increase in the abnormal values will be noted in all groups. The rats on the liver diets showed many more abnormal values than did those on stock diet 2.

To demonstrate the evolution of the changes in the albumin content of the urine, we have constructed figures 2 to 5. In these graphs the curves represent the averages for the monthly albumin values of all the animals within a group. The number of animals used and the group curves are given in the graphs.

Figures 2 and 3 show clearly the marked differences in behavior between male and female rats. It will be noted that all groups started with normal values. Increased albumin values occurred earlier and reached higher maxima in groups of male rats than in the corresponding groups of females.

Figure 4 is drawn from the data given in table 5 and shows the striking effect of thyroid when added to a nephritis-inducing diet. The rapid onset and evolution of the disease when 0.4 per cent thyroid was given were in marked contrast to the gradual change that occurred with 0.1 per cent thyroid. The average length of life of the animals was one hundred and forty-eight days with 0.4 per cent thyroid and five hundred and thirty-nine days with 0.1 per cent thyroid. All the data indicated that the feeding of the larger quantity of thyroid resulted in producing severe nephritis, which we believe contributed significantly to shortening the average length of life.

In figure 5 it will be noted that in nephrectomized rats the liver diets produced a more rapidly developing and a more severe albuminuria than did the stock diet

The first casts to appear in the urine of rats were often pigmented. Granular casts were commonly present in cases of developing nephritis. Later, hyaline casts were present, and in the final stages highly refractive casts appeared. Cylindroids were often associated with the casts. Red blood corpuscles were not present except in the case of rats fed yeast diet 1. It will be recalled that all these animals had renal calculi. Crystals of dicalcium hydrogen phosphate were commonly present in the urinary sediment of rats fed irradiated yeast, but they were never observed in the specimens from rats given other diets

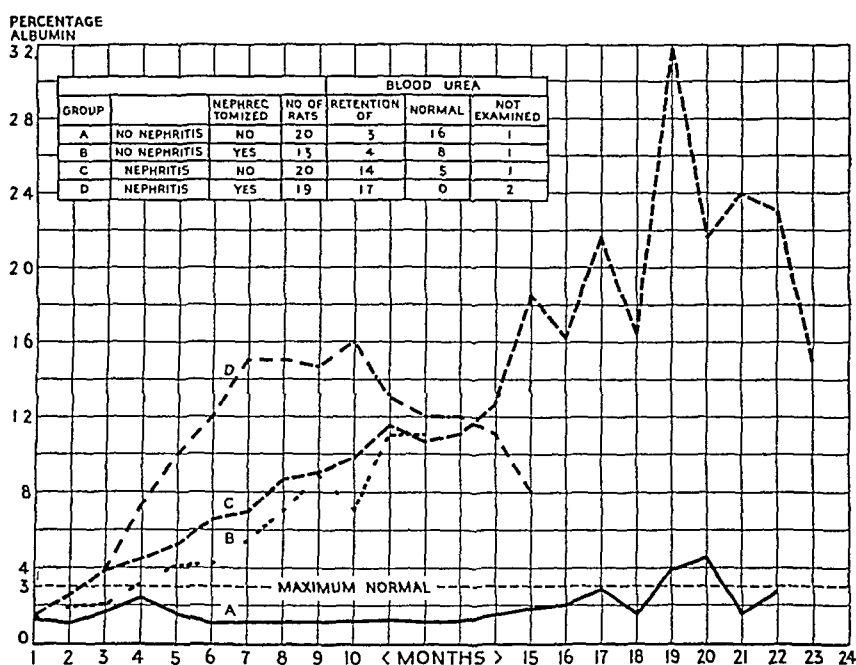


Fig 2—Chart showing the excretion of albumin and the retention of urea in male rats with 3 plus or 4 plus nephritis and in male rats without nephritis

BLOOD PICTURE

Urea Retention—We have considered 30 mg per hundred cubic centimeters as the upper limit of normal for the urea nitrogen content of the blood of the rat. Thirty-nine rats which were found to have 3 plus nephritis gave an average value of 61.4 mg, the highest value being 221 mg per hundred cubic centimeters. Twenty-three (59 per cent) of the values were above the normal limit. In the case of 85 rats with 4 plus nephritis, the average value was 141 mg, and the highest value was 375 mg per hundred cubic centimeters. Not a single case of nonretention was observed in this series. It is evident that the histologic classification of the extent of nephritis was in accord

with the degree of urea retention. Among the 40 intact rats without nephritis, there were 3 (7.5 per cent) instances of retention. Six (20 per cent) of 30 nephrectomized animals without nephritis showed retention. This difference is significant and indicates that one kidney has difficulty in performing adequately the function of forming normal urine. The observations, as a whole, show that renal injury must be severe before retention of nitrogenous products consistently occurs.

Albumin-Globulin Ratio—In certain types of nephritis the quantities of albumin and globulin in the blood plasma are changed so that this ratio is decreased. Such a change is found in the chronic active stage of hemorrhagic nephritis and is marked in cases of nephrosis. We have considered values for this ratio of less than 1 to be abnormal.

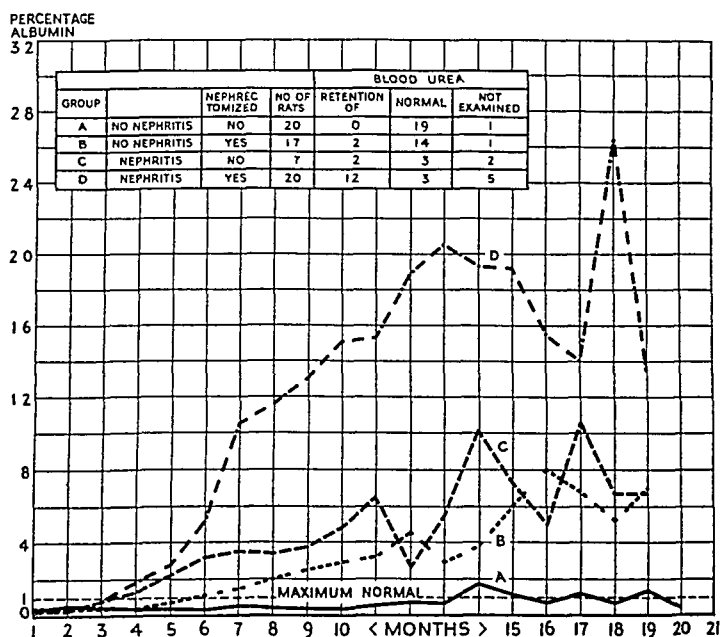


Fig. 3—Chart showing the excretion of albumin and the retention of urea in female rats with 3 plus or 4 plus nephritis and in female rats without nephritis.

In a series of 22 rats with 3 plus or 4 plus nephritis, all but 1 showed an abnormal ratio. Our study of the pathogenesis of nephritis revealed that only 1 (4.8 per cent) of 21 female rats fed stock diet 2 had a ratio of less than 1, while 6 (35.3 per cent) of 17 had a low ratio when fed the liver diets. Six (37.5 per cent) of 16 male rats fed stock diet 2 had an abnormal ratio, and 10 (66.7 per cent) of 15 had an abnormal ratio when fed liver. Apparently, the albumin-globulin ratio is more easily disturbed in males. Several cases of inversion of the ratio in rats without nephritis were observed, and this indicates that factors other than nephritis influence the concentration of protein in the blood.

Cholesterol—The cholesterol content of the blood plasma has been observed to increase in conditions in which there is an inversion of

the albumin-globulin ratio. It is believed that this increase in the cholesterol content is the result of an effort to maintain the normal osmotic relationships of the blood. We have found it necessary to establish two maximum normal limits for the cholesterol content of the blood of our rats, owing to the fact that the cholesterol contained in liver diets increases the content of this substance in the blood. The average value for the plasma cholesterol of 31 rats without nephritis which were fed stock diet 2 was 88 mg per hundred cubic centimeters, the mean deviation being 29.2 mg. Therefore, it has been considered that values over 146 mg per hundred cubic centimeters for rats fed liver-free diets indicate hypercholesteremia. Similarly, 88 rats without nephritis which were fed liver diets gave a mean value of 125.5 mg

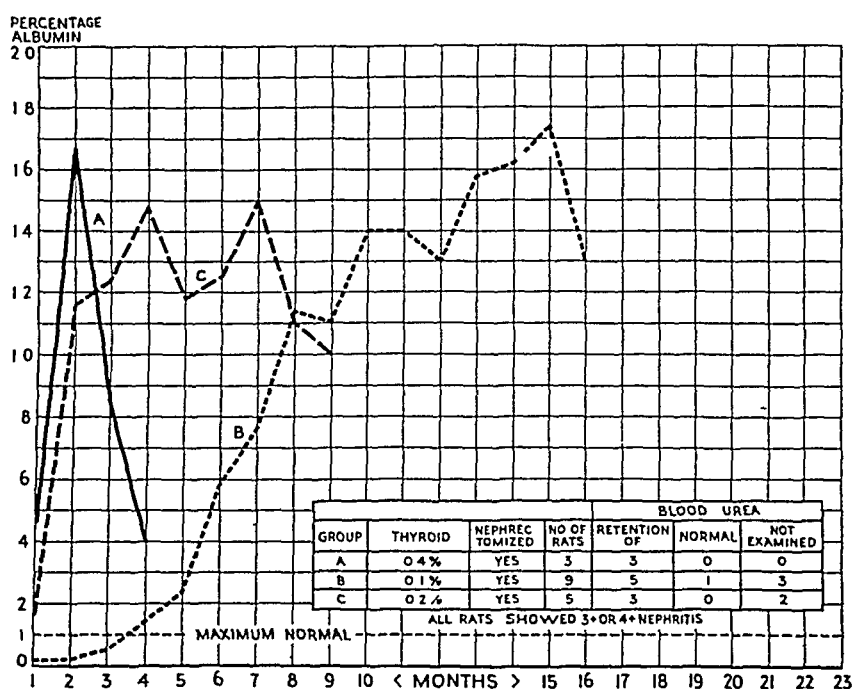


Fig 4—Chart showing the excretion of albumin and the retention of urea in female rats fed liver diet plus thyroid

per hundred cubic centimeters. Twice the mean deviation of 46.7 mg indicates that 219 mg per hundred cubic centimeters should be taken as the upper limit for the normal cholesterol content when liver diets are concerned. The results for rats fed nonliver diets were as follows: 5 (50 per cent) of 10 with 3 plus nephritis showed hypercholesteremia, and 7 (87.5 per cent) of 8 with 4 plus nephritis showed values above the normal limit. The following results were obtained for the animals fed diets containing liver: Fifteen (41.7 per cent) of 36 having 3 plus nephritis had hypercholesteremia, and 34 (51.5 per cent) of 66 with 4 plus nephritis showed values above normal. The values for rats with nephritis were in general agreement with the changes observed in the albumin-globulin ratio.

In our study of the pathogenesis of nephritis 4 (11.1 per cent) of 36 rats fed stock diet 2 had hypercholesteremia, 2 of these had 4 plus nephritis, with retention of nonprotein nitrogen, and the others had no nephritis and showed no retention. Three (9.4 per cent) of 32 animals fed the liver diets accumulated cholesterol in the blood, 2 of these had retention of nonprotein nitrogen and 2 plus nephritis, and the other with 1 plus nephritis had no retention.

If the values for cholesterol are considered in relation to calcification of the aorta, it will be seen that 18 animals with calcification of the aorta gave an average value of 182 mg of cholesterol per hundred cubic centimeters of blood, the range being from 87 to 290 mg. These results show that the calcification was not due to an abnormally high cholesterol content of the blood.

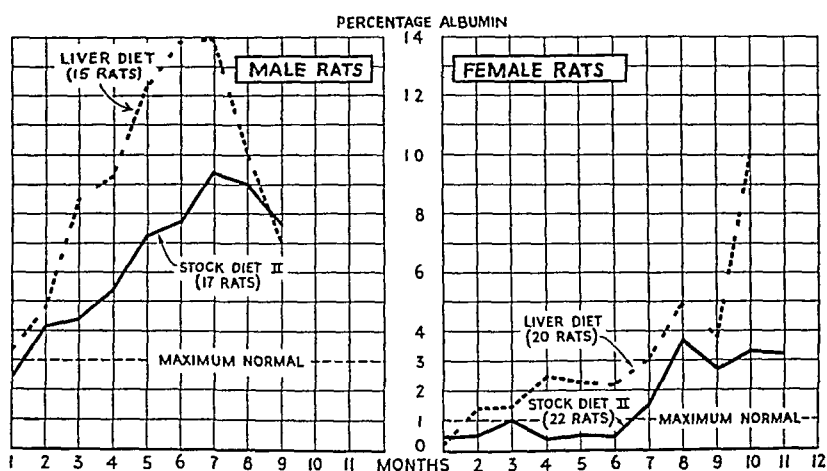


Fig 5—Chart showing the excretion of albumin in nephrectomized male and female rats fed liver diets 1 and 3 and stock diet 2

COMMENT

The present concept of the etiology of chronic nephritis is necessarily in a confused state. One group of workers think that infection superimposed on a preexisting state of allergy initiates the degenerative process, another group, in which are Newburgh and his associates, believe that dietary factors play an essential rôle. That the nephritis produced experimentally in our rats was not dependent on the existence of infectious processes is evident from the following observations: (a) The organs most frequently infected were the lungs, but there was no higher incidence of nephritis in animals with marked pulmonary involvement than in those free from it, (b) in the rats on diet 2899 local infection in the mouth secondary to erosion of the mucosa by overgrowth of the upper incisors occurred often but there was no nephritis among these animals, (c) in the group of rats in

which hydronephrosis developed while they were receiving a diet containing irradiated yeast practically no renal infection and but little nephritis were present, although urinary retention was sometimes marked and was often accompanied with inflammation of the wall of the bladder and with severe ulceration of the mucosa induced by calculi

Our results herein reported have shown conclusively that diet alone will produce nephritis and will also determine its severity. We cannot at present explain how the diet produces these effects.

That the injurious principle is not confined to the protein content of the diet may well be. From a purely theoretical point of view certain diets may possibly aid in establishing abnormal complex metabolic processes which lead to the formation of abnormal products or of increased normal end-products, to the overfiltration of the normal end-products, to the excretion of the abnormal products or to the retention of certain products. Whatever these substances are that pass the glomerular filter, it is conceivable that they may have existed as such in the diet or that they may have been produced within the body during metabolism. From the urinary findings it seems that an abnormal functional condition of the kidney considerably antedates the appearance of histologic evidence of nephritis.

From our experience it is evident that the greatest care must be used in the planning and compounding of experimental diets, for the overlooking of a seemingly minor factor may lead to unsuspected complications and to erroneous conclusions relative to the effects produced. Thus the cooking of diet 2899 eliminated the development of abnormalities of the teeth and bones, the substitution of irradiated for non-irradiated yeast led to hydronephrosis, calcification of the aorta and the formation of renal calculi, and the addition of thyroid to the diet favored the production of nephritis and of calcification of the aorta. By reducing the quantity of thyroid the development of nephritis was delayed, and the average length of life of the rats was increased. Further studies on the effects of the administration of thyroid are now in progress. Obviously, a diet that has been proved to be satisfactory for the growth and well-being of the type of animal used should always be employed as a control.

In such experimental work as ours attention must be paid to the gross and microscopic examination of the various types of tissue and must not be limited to a consideration of a single organ, such as the kidney or liver. This became apparent early in these studies, when we found that during the first few weeks we could identify the rats fed liver diet 1 by the fatty infiltration in the liver while the kidneys appeared normal. Abnormalities in other organs cannot always be

correlated with the most important pathologic process produced, but they tend to show that the body as a whole may be involved rather than any one tissue or organ

A peculiar and interesting fact which we discovered is that the female rat is more refractory to the production of nephritis by diet than the male. This was well shown by intact rats fed identical diets, in 21 per cent of the males marked nephritis developed, while only 6 per cent of the females showed a similar condition. Whether this difference is confined to the rat is unknown. May it not pertain to the sexes in other species? Sex differences in the glycogen content of the tissues and in the metabolism of fat also have been observed. Nature may have evolved distinct metabolic differences between the male and the female, perhaps to enable the latter better to fulfil her special functions.

The extreme disorders of calcium metabolism induced by diets containing irradiated yeast deserve special consideration. Other investigators have reported the formation of renal calculi and the deposition of calcium in the tissues resulting from the administration of toxic doses of vitamin D. However, we were rather surprised to find that such changes could be produced so consistently by the quantity of irradiated yeast fed to our rats. These observations suggest that the indiscriminate use of the many irradiated products now available may be the source of unfortunate complications later.

The changes noted in the blood constituents were in general agreement with those observed in human beings with nephritis. It was found that retention of urea did not occur until injury to the kidney had become severe. Our data for the albumin-globulin ratio showed it to be disturbed in a large majority of the rats with severe nephritis, and there were indications that it is more easily changed in male than in female rats. The observed increases in the cholesterol content of the blood harmonized with the concomitant decreases in the albumin-globulin ratio. Rats in which calcification of the aorta had developed did not have hypercholesteremia. Unfortunately, none of these determinations is useful in detecting early functional changes in the kidney.

Our data suggest that irreparable renal damage occurs only as the end-result of an interaction of unknown factors which have existed for a considerable period of time. These unknown factors, our ignorance of how they are interrelated and the uncertainty concerning the changes which occur between the initiation of the process and the appearance of the irreparable damage greatly hinder at this time an explanation of the pathologic process. If one considers the evidence of functional derangement of the kidney, as shown by the appearance of abnormal quantities of albumin and of casts in the urine, it is apparent that the

functional impairment antedates the appearance of histologic changes by a considerable period. If it is assumed that the initial impairment occurs in the functional activity of the glomerulus as a filter, it may be deduced that the tubular epithelial cells, in their efforts to conserve portions of the filtered plasma eventually reach a state in which they in turn become functionally overworked, when such a condition is reached they apparently disintegrate. At about this time an inflammatory reaction ensues, as evidenced by lymphocytic infiltration and fibrosis. The accumulation in the tubule of material which has passed the glomerular filter occurs later, after the periods of epithelial hyperplasia, inflammation and fibrosis. It is somewhat uncertain just where in the tubule the epithelium suffers the most damage, but from the location of the cellular hyperplasia, the staining reaction of the epithelial cells and the retention of urinary secretion the injury seems to be restricted principally to the distal portion. Why the distal portion should be impaired rather than the proximal portion is not clear, the answer to this question must be deferred pending a better understanding of the function of the epithelium along the course of the tubule. Our observation that in rats the irreparable damage is restricted to a certain portion of the tubule is in agreement with Richards'¹⁰ observation that in the frog and in *Necturus* the epithelium of the proximal portion differs functionally from that of the distal end.

The data presented clearly demonstrate that casts and abnormal quantities of albumin appeared earlier in nephrectomized rats in which severe nephritis ultimately developed than in the animals in which nephritis failed to develop, the output of albumin was greater, and there was a tendency for it to decline toward the end of the disease, probably because of the destruction of many glomeruli. These same phenomena were present in the intact rats, but in these they occurred later and less abruptly. It should be noted that casts were at times absent from the urine even when severe nephritis was present, certainly the number of casts was no true index of the severity of the nephritis, as it varied from time to time while the disease was actively progressing.

The significance of the abnormal urinary findings deserves special consideration. It is apparent that an increase in the albumin content or the presence of casts does not necessarily indicate pathologic nephritis. Such findings do indicate a functional impairment of the kidney which may or may not terminate in irreparable renal damage. In nephrectomized animals fed stock diet 2, with persistent evidence of functional impairment, severe nephritis did not develop, even though the animals lived for two years after the operation. The influence of

¹⁰ Richards, A. N. *Urine Formation in the Amphibian Kidney*, Harvey Lectures, 1934-1935, Baltimore, Williams & Wilkins Company, 1936, p. 93.

diet on the functional activity of the kidney is clearly shown in figure 5. Here the function of the remaining kidney was disturbed in all groups, but the nephritis-inducing diets caused a greater functional disturbance than did the harmless stock diet 2. Obviously, a single kidney cannot carry the functional load as well as the two organs which nature has provided. It is to be hoped that a method may be found by which it will be possible to recognize functional impairment before permanent structural damage has occurred, since it may be possible to cure the former, even though it may not be possible to prevent further degeneration in a kidney once permanent damage has been established.

SUMMARY

Chronic nephritis has been produced in rats by feeding them diets high in protein. The evidence presented has shown that functional impairment of the kidney may exist for some time before histologic changes indicative of nephritis become apparent. The excretion of albumin or the presence of casts in the urine was interpreted as indicating functional impairment of the kidney, although not necessarily proving the presence of nephritis. When irreparable damage occurred, retention of nonprotein nitrogen, inversion of the albumin-globulin ratio and hypercholesteremia were observed.

It was found that female rats were more refractory to the production of nephritis by diet than males. The addition of desiccated thyroid to the diet of nephrectomized females favored the development of nephritis. The feeding of irradiated yeast led to hydronephrosis, calcification of the aorta and the formation of renal calculi. Calcification of the aorta was not associated with hypercholesteremia.

We have suggested that the initial impairment of the kidney may be a change in the functional activity of the glomerulus. The filtering of unusual substances into the tubule throws an additional strain on the distal epithelial cells, causing them finally to disintegrate. An inflammatory reaction ensues. Material which passes through the glomerulus is then dammed back into the proximal tubule and causes cystic dilatation. Judging from the location of the cellular hyperplasia, the staining reaction of the epithelial cells and the retention of urinary secretion, the primary injury to the tubular epithelium seems to be limited principally to the distal portion. The entire process may be looked on either as a result of overwork or as a toxic phenomenon.

The injurious factor may exist as such in the diet, or it may be produced during metabolism. If the harmful substance exists in the diet, it may not necessarily be confined to the protein fraction. The nephritis may be induced by an abnormal excretion of normal end-products, by an excretion of abnormal products or by the retention of certain products.

ACUTE VEGETATIVE ENDOCARDITIS CAUSED BY BACILLUS DIPHTHERIAE

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Acute vegetative endocarditis caused by the diphtheria bacillus is of infrequent occurrence, the literature up to the present time containing reports of only six cases. The micro-organisms isolated in three of these cases had all the cultural and morphologic characteristics of *Bacillus diphtheriae* but did not produce a toxin in amounts sufficient to be lethal for guinea-pigs. In the other three cases reported the bacilli were characteristic of *B. diphtheriae* morphologically and culturally as well as in their lethal effect when broth cultures were injected into guinea-pigs.

The nontoxic bacilli simulating *B. diphtheriae* were isolated at autopsy in the cases reported by Howard¹ in 1893 and by Roosen-Runge² in 1903 and 1925. Herzog³ in 1918 was the first to isolate a strain of *B. diphtheriae* from the blood in pure culture which was lethal for guinea-pigs when 1 cc of a three day broth culture was inoculated subcutaneously. The bacilli isolated from the two patients reported on by Chiari⁴ in 1933 and 1935 also were typical in their lethal effect on guinea-pigs when broth cultures were inoculated subcutaneously. A patient with this type of endocarditis came to autopsy recently at the Vanderbilt Hospital, and a detailed report of the case follows.

REPORT OF A CASE

The patient, a 16 year old boy, was admitted to a medical ward four months before his death. He complained of frequent, moderately severe nosebleeds,

From the Department of Pathology, the Vanderbilt University Medical School

1 Howard, W T, Jr. Acute Ulcerative Endocarditis Due to the *Bacillus Diphtheriae*, *Bull Johns Hopkins Hosp* 4 32, 1893

2 Roosen-Runge. Ein Fall von Diphtheriebazillensepsis, *Munchen med Wchnschr* 50 1252, 1903, Ueber Bakteriämie durch Diphtheriebazillen, *Virchows Arch f path Anat* 254 379, 1925

3 Herzog, G. Demonstration einer ulzerösen Endokarditis durch Diphtheriebazillen, *Munchen med Wchnschr* 65 29, 1918

4 Chiari, H. Zur Frage der Diphtherie-Endokarditis, *Centralbl f allg Path u path Anat* 58 193, 1933, Zur Frage des Uebertretens der Diphtheriebazillen in die Blutbahn und ihrer Ansiedlung in inneren Organen, *Wien klin Wchnschr* 48 685, 1935

which had their onset about three months previous to his admission to the hospital. He had an attack of rheumatic fever at the age of 7 years without any appreciable sequelae. His father and one uncle had had spontaneous nosebleeds over a period of one year during adolescence.

Physical examination revealed that the boy's heart was moderately enlarged to the left, the spleen was palpable and there were numerous cutaneous telangiectases scattered over the body. Studies of the blood revealed nothing abnormal, except a low platelet count, from 40,000 to 130,000 per cubic millimeter. The bleeding time, clot retraction and tourniquet tests were normal. No definite diagnosis as to the cause of the nosebleeds could be made during the patient's first stay of two months in the hospital. During this time he had a few mild nosebleeds, which were controlled by packing. He had a low grade continuous fever. He was sent home and remained there for six weeks. He continued to have occasional mild nosebleeds. Two days before his second admission to the hospital a severe nosebleed occurred which necessitated packing. Attempts to remove the pack brought on severe bleeding, so that it had to be replaced. At that time the nasopharynx was tender, and the pack had a foul odor. Other physical and laboratory findings were much the same as at the previous entry, except that gradual enlargement of the spleen and liver was observed. During the next ten days he had three severe nosebleeds, which were controlled by packing. Five days before his death the temperature suddenly rose from 102 to 105 F. Culture of the blood was positive for an unidentified gram-positive bacillus, which grew 142 colonies per cubic centimeter. Enlargement of the heart to the left rapidly developed together with ascites. A systolic and diastolic murmur developed. During the last twenty-four hours numerous petechial hemorrhages appeared over the body. The patient was anuric for thirty-six hours preceding death. The nonprotein nitrogen content of the blood rose to 92 mg per hundred cubic centimeters.

At autopsy the heart weighed 440 Gm. There were moderate hypertrophy and dilatation of the left ventricle. A large friable fibrinous vegetation extended along the edges of the mitral valve (fig 1A). The leaflets of the valve were scarred, and their edges were rolled and thickened. Direct smears from the vegetation showed innumerable long, slender bacilli, which were irregular in shape and form and showed a tendency to be arranged in parallel rows. They were chiefly gram-positive, but many of them decolorized readily (fig 1C). Stained with Löffler's methylene blue, metachromatic bipolar granules, characteristic of the diphtheroids, could be demonstrated. Microscopic section of the valve showed the valvular endothelium to be ulcerated, and from its edge extended a dense thrombotic mass, consisting chiefly of micro-organisms bound together by fibrin and a few polymorphonuclears (fig 1B). In sections stained by the Gram method these organisms were not decolorized.

Other significant features were noted microscopically. There was acute arteritis in the smaller vessels of the heart, lungs, intestine and skin, characterized by hyaline necrosis of the intimal layer and perivascular collections of polymorphonuclears and monocytes. Occasionally a hyalinized thrombus was seen within the lumen of an arteriole. There was acute splenitis characterized by hyaline necrosis of the centers of all the malpighian corpuscles. Acute embolic nephritis and acute interstitial orchitis also were present. There were marked hemorrhages in the adrenal capsules.

Growth Characteristics of the Micro-Organism—A pure culture of the bacillus was obtained from the heart blood, the mitral vegetation and the spleen under aerobic and anaerobic conditions. The organisms appeared in all instances as



Fig 1—*A*, section of the heart, showing ulceration and vegetation of the mitral valve *B*, section from the mitral valve showing extensive vegetation, consisting chiefly of micro-organisms *C*, smear preparation from the mitral vegetation showing micro-organisms Gram stain, $\times 2,000$ *D*, smear preparation from a twenty-four hour broth culture stained by the Neisser method, showing metachromatic bipolar granules, $\times 2,000$ *E*, smear preparation from a twenty-four hour culture of the organism on the chorio-allantoic membrane of a chick embryo Wright stain, $\times 2,000$

pleomorphic, short, fat bacilli, which tended to be arranged in picket fence formation. Stained by the Gram method, the organisms were easily decolorized. Many gram-negative forms were present, although the majority were gram-positive. A twenty-four hour broth culture showed granular growth which settled to the bottom of the tube, but by subsequent culture the organisms were easily induced to form a pellicle on the surface of this medium. Subcultured on Löffler's medium, a twenty-four hour culture showed numerous grayish white, glistening colonies. Colonies on 10 per cent blood agar showed no hemolysis. After twenty-four hours small, round, opaque, white, glistening colonies appeared, each with the center heaped-up and the entire edge smooth. The bacillus fermented dextrose, lactose and maltose, with acid and without gas. No fermentation occurred in sucrose. Smears from these subcultures showed pleomorphic granular bacilli which had an irregular staining capacity. By the Gram method they were readily decolorized, but when stained by the Neisser method metachromatic bipolar granules were readily demonstrated (fig 1D). A tendency to arrangement in parallel rows, curved forms and clubbed ends was evident.

The organisms cultured on artificial mediums, however, showed marked differences from those obtained by direct smear from the mitral vegetation. The organism obtained by direct smear at autopsy was much longer and more slender than the shorter pleomorphic form obtained by culture on artificial mediums. A loopful of a twenty-four hour broth culture was inoculated on the chorio-allantoic membrane of several 12 day old chick embryos. The bacilli multiplied rapidly and caused the death of the embryo within twenty-four hours. Smears made from the infected membrane showed long, slender granular rods in parallel arrangement, much more closely resembling those seen in the smear made directly from the valve (fig 1E).

Animal Inoculations—Twenty-four hour broth cultures were inoculated subcutaneously in 2 cc amounts into two guinea-pigs weighing 250 Gm, each, one of which had received 300 units of standard diphtheria antitoxin twenty-four hours previously. The unprotected guinea-pig died within forty-eight hours, the protected animal experienced no ill effects. Intraperitoneal inoculation of 0.25 cc of a twenty-four hour broth culture caused death in an unprotected guinea-pig in three days. A control animal, protected twenty-four hours previously with 300 units of standard diphtheria antitoxin, survived.

Virulence tests, performed by making intracutaneous inoculations into guinea-pigs of 0.1 cc amounts of undiluted culture and 1:5, 1:10, 1:20, 1:50 and 1:100 dilutions of a twenty-four hour broth culture gave positive reactions which went on to severe necrosis up to dilutions of 1:50. Control guinea-pigs, protected by 300 units of standard diphtheria antitoxin, showed no reaction.

The bacillus was cultured also in shallow flasks of nutrient broth over a period of seven days in order to determine whether or not a toxin was produced. The sterile Berkefeld V filtrate from a seven day old broth culture was injected in 0.1 cc amounts intracutaneously into normal guinea-pigs and into guinea-pigs protected by a twenty-four hour injection of 300 units of diphtheria antitoxin. Positive reactions which progressed to severe necrosis were obtained in the normal animals with dilutions up to 1:20. The protected animals showed no reaction.

COMMENT

From all the available evidence it can be stated that this report adds another to the few cases of vegetative endocarditis caused by the *B. diphtheriae* recorded thus far in the literature. Morphologically and

culturally the organism isolated in this case belonged to the group *Corynebacterium*. Intracutaneous tests in guinea-pigs with a twenty-four hour broth culture and the filtrate of a seven day broth culture produced reactions typical of *B. diphtheriae*. Subcutaneous and intraperitoneal inoculations of the twenty-four hour broth culture caused death in an animal within three days. The administration of standard diphtheria antitoxin by the standard method protected guinea-pigs against the effect of the organism. These findings prove that the organism isolated from the mitral valve was a true strain of *B. diphtheriae*.

The portal of entry in this case most likely was the ulceration of the nasopharynx, which was caused by the prolonged packing necessitated by the continuous nosebleeds. The mitral valve, previously damaged by rheumatic disease, apparently provided a favorable lodging place for the organism, which gained entry to the blood stream from the ulcerated nasopharynx. From here embolic lesions were set up in the heart, intestines, kidneys, skin and mucous membranes. From the clinical course in this case it is obvious that the endocarditis was rapid and fulminating, lasting probably for only five days.

SUMMARY

A case of acute vegetative mitral endocarditis caused by *B. diphtheriae* is reported.

The bacillus isolated in pure culture from the heart blood, mitral vegetation and spleen at autopsy had the morphologic and cultural characteristics of *B. diphtheriae*. Inoculations into guinea-pigs demonstrated its toxin-producing capacity. Its toxic effect for guinea-pigs could be neutralized by the administration of standard diphtheria antitoxin.

CLINICAL SIGNIFICANCE OF BACTEREMIA IN PNEUMOCOCCIC PNEUMONIA

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This paper is concerned with an analysis of 1,586 cases of pneumonia associated with specific pneumococci of types I to XXXII (Cooper¹) in which cultures of the blood were made during the acute stage of the disease or at autopsy. The purpose of this study is to correlate the incidence of bacteremia and the death rate with the more common factors known or supposed to influence the prognosis, including (1) the type of pneumococcus, (2) the age of the patient, (3) the sex, (4) the character of the pulmonary lesion, (5) the extent of the pulmonary involvement, (6) alcoholism, (7) preexisting diseases and conditions and (8) the leukocyte count. The effect of bacteremia on the incidence of septic complications and on the duration of the acute stage of the disease in cases of uncomplicated pneumonia is noted. The incidence of positive blood cultures on different days of the disease is correlated with the death rate. Variations in the results of multiple blood cultures during life and at autopsy are considered.

Few of these matters have received adequate consideration in the literature, except the comparative death rates for patients with pneumonia as regards the presence of bacteremia and occasional correlations with the types of pneumococcus. Most of the latter studies, furthermore, lose much of their value because the types were not adequately identified.

MATERIAL AND METHODS

The cases included in this analysis satisfy the following criteria: (1) the patients were 12 years of age or older and were admitted to the medical services of the Boston City Hospital between Nov. 1, 1929, and May 31, 1935, (2) definite

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1 Cooper, G., Rosenstein, C., Walter, A., and Peizer, L. The Further Separation of Types Among the Pneumococci Hitherto Included in Group IV and the Development of Therapeutic Antisera for Those Types, *J. Exper. Med.* **55**: 531 (April) 1932.

evidence of pneumonia was demonstrated by physical signs, and except in occasional instances this was verified by roentgenograms or by postmortem examination or both, (3) pneumococci which agglutinated specifically in one of the antipneumococcus serums of types I to XXXII were isolated and identified from some source which suggested its etiologic relation to the pneumonia, namely, the sputum, blood or pulmonary or pleural fluid,² and (4) cultures of the blood were made on one or more occasions during the acute febrile stage of the illness and/or at necropsy. Patients having septic postpneumonic complications, such as empyema or pulmonary abscess, at the time of admission to the hospital were excluded.

A total of 2,448 blood cultures were made in the 1,586 cases. These included 382 cultures of heart blood taken postmortem, this being the only blood culture made in 210 of the cases. Cultures of venous blood were made at the bedside by introducing 5 or 10 cc into 100 cc of beef infusion broth (p_H 7.8), with 0.1 per cent dextrose added. Pour plates for colony counts were made in about half the cases, either by introducing 1 cc (or smaller amounts when indicated) into 10 cc of agar at the bedside or by using citrate as an anticoagulant and making the pour plates with 1 or 2 cc of blood in the laboratory. At postmortem examination blood was obtained from the inferior vena cava within the pericardial cavity and was placed in broth and on blood agar plates. All pneumococci were isolated in pure culture and identified by morphologic and cultural characteristics, bile solubility and specific agglutination in antipneumococcus serums, either macroscopically or microscopically.³ Serums for types I to XX only were available until May 1932 and for types I to XXXII thereafter. Throughout this study the cases are divided into two large groups: (1) the cases in which bacteremia was present—pneumococci were grown in culture of the blood *at some time* and (2) the cases in which bacteremia was not noted—all the blood cultures remained sterile. In most instances the cases in which specific antipneumococcus serums were used are considered separately.

RESULTS

The data will be presented chiefly in tabular form, supplemented by brief summaries and explanatory remarks.

Incidence of Bacteremia and the Mortality by Types (table 1) — Each of the specific serologic types of Cooper¹ was represented, although for a number of types there were too few cases to be significant and some of the latter included no cases in which bacteremia was present. For each type the death rate in the cases in which blood culture was positive was two or more times as high as in the cases in which the blood cultures were sterile, and for all types it averaged almost three times as high. For only a few of the types was the number of cases sufficiently large to warrant deductions with respect to variations in the incidence of bacteremia and in the mortality. From the data for these types, however, it appears that they may vary con-

2 Finland, M. The Significance of Mixed Infections in Pneumococcic Pneumonia, J. A. M. A. **103** 1681 (Dec 1) 1934.

3 (a) Avery, O. T., Chickering, H. T., Cole, R., and Dochez, A. R. Acute Lobar Pneumonia. Prevention and Serum Treatment, Monograph 7, Rockefeller Institute for Medical Research, Oct 16, 1917. (b) Sabin, A. B. The Microscopic Agglutination Test in Pneumonia, J. Infect. Dis. **46** 469 (June) 1930.

siderably Positive results of blood cultures were obtained in slightly more than a third of all the cases The incidence of bacteremia varied widely in the cases of different types and was highest for the cases of pneumonia due to type II pneumococci In the fatal cases the incidence of bacteremia was four times as great as for the nonfatal cases, and

TABLE 1—Incidence of Bacteremia and Mortality According to the Type of *Pneumococcus*

Type of Pneumo- coccus	Treat- ment with Serum	Blood Cultures											
		Positive			Negative			All Cases			Positive, %		
		No of Cases	Fatal Cases	Fatal Cases, %	No of Cases	Fatal Cases	Fatal Cases, %	No of Cases	Fatal Cases	Fatal Cases, %	All Cases	Fatal Cases	Non fatal Cases
I	S	69	25	36	123	15	12	192	40	21	36	63	29
I		123	104	86	142	37	26	265	141	53	47	74	15
II	S	31	20	65	47	6	13	78	26	33	40	77	21
II		62	47	76	45	14	31	107	61	57	58	77	33
III		118	116	98	144	58	40	262	174	66	45	67	2
IV		15	14	93	21	6	29	36	20	56	42	70	6
V		39	34	87	61	17	28	100	51	51	39	67	10
VI*		3	2	67	21	10	48	24	12	50	12	17	8
VII	S	2	1	50	8	0	0	10	1	10	20	100	11
VII		23	21	91	54	9	17	77	30	39	29	70	11
VIII		46	24	52	93	29	31	139	53	38	33	45	4
IX		4	3	75	21	6	29	25	9	36	16	33	26
X		6	5	83	30	14	47	36	19	53	17	26	6
XI		2	1	50	17	5	29	19	6	32	11	17	8
XII		10	8	80	18	3	17	28	11	39	36	73	12
XIII		3	2	67	12	4	33	15	6	40	20	33	11
XIV		9	8	89	24	9	32	33	16	48	27	50	6
XV		0	0		9	5	56	9	5	56	0	0	0
XVI		1	1	100	2	0	0	3	1	33	33	100	0
XVII		0	0		13	5	38	13	5	38	0	0	0
XVIII		7	7	100	26	11	42	33	18	55	21	39	0
XIX		1	1	100	15	2	13	16	3	19	6	33	0
XX		4	4	100	29	8	28	33	12	36	12	33	0
XXI		0	0		7	1	15	7	1	15	0	0	0
XXII		1	1	100	11	5	45	12	6	50	8	17	0
XXIII		1	1	100	1	1	100	2	2	100	50	50	
XXIV		0	0		1	0	0	1	0	0	0		0
XXV		1	0	0	0	0		1	0	0	100		100
XXVII		1	1	100	0	0		1	1	100	100	100	
XXVIII		0	0		2	1	50	2	1	50	0	0	0
XXIX		0	0		3	2	67	3	2	67	0	0	0
XXX		0	0		1	0	0	1	0	0	0	0	0
XXXI		0	0		2	0	0	2	0	0	0	0	0
XXXII		0	0		1	0	0	1	0	0	0	0	0
Serum treatment		102	46	45.1	178	21	11.8	280	67	23.7	36.4	68.7	26.3
No serum treatment		450	405	84.4	826	261	31.6	1,306	666	51.4	36.8	60.8	11.7
Total		552	451	77.5	1,004	282	28.1	1,586	733	46.2	36.7	61.5	15.4

* This type includes types VIa, VIb and XXVI, designations which are no longer used

this proportion was even higher when the cases in which serum treatment was given were excluded

These findings are similar, in general, to those of Bullowa and Wilcox,⁴ who noted that "in the main the percentages of invasiveness and mortality are approximately the same" The higher death rates consistently recorded in the present report were probably due to the selection of cases, since we excluded all nonfatal cases in which no

4 Bullowa, J G M, and Wilcox, C Incidence of Bacteremia in the Pneumonias and Its Relation to Mortality, Arch Int Med 55 558 (April) 1935

blood cultures were made before the crisis and included many cases of bronchopneumonia and also cases in which the type was first determined at necropsy. The age distribution in this series also may have contributed to the higher mortality, as children were excluded, and

TABLE 2—Incidence of Bacteremia and Mortality According to Age and Sex

Age Group	Blood Cultures									Positive, %
	Positive			Negative			All Cases			
	Number of Cases	Fatal Cases	Fatal Cases, %	Number of Cases	Fatal Cases	Fatal Cases, %	Number of Cases	Fatal Cases	Fatal Cases, %	
12 19	22	6	27	124	10	8	146	16	11 0	15 1
20 29	58	32	55	177	22	12	235	54	23 0	24 7
30 39	88	53	60	209	27	13	297	80	26 9	29 6
40 49	137	107	78	182	46	25	319	153	48 0	42 9
50 59	106	91	86	172	81	47	278	172	61 9	39 1
60 69	107	98	92	72	39	54	179	137	76 5	59 8
70 +	64	64	100	68	57	84	132	121	91 7	48 5
Total	582	451	77 5	1,004	282	28 1	1,586	733	46 2	36 7
Males	408	314	77 0	705	185	26 2	1,113	499	44 8	36 7
Females	174	137	78 7	299	97	32 4	473	234	49 5	36 6

TABLE 3—Bacteremia in the More Common Types According to Age

Type of Pneumococcus	12 to 29 Years Blood Cultures						30 to 49 Years Blood Cultures						50 Years or More Blood Cultures					
	Positive			Negative			Positive			Negative			Positive			Negative		
	Fatal Cases, %			Fatal Cases, %			Fatal Cases, %			Fatal Cases, %			Fatal Cases, %			Fatal Cases, %		
	No of Cases	Fatal Cases	Positive, %	No of Cases	Fatal Cases	Fatal Cases, %	No of Cases	Fatal Cases	Positive, %	No of Cases	Fatal Cases	Fatal Cases, %	No of Cases	Fatal Cases	Positive, %	No of Cases	Fatal Cases	Fatal Cases, %
I*	23	3	13	29	56	3	32	14	44	33	52	6	12	14	8	57	48	15
I	14	8	57	20	44	3	51	40	78	45	63	10	16	53	56	97	62	35
II*	8	5	62	26	23	0	15	9	60	48	16	3	19	8	6	75	50	8
II	8	4	50	32	17	4	27	19	70	61	17	3	18	27	24	89	71	11
III	5	5	100	20	20	1	27	26	96	34	52	12	23	86	85	99	54	72
IV	2	2	100	29	5	0	6	5	83	37	10	2	20	7	7	100	54	6
V	7	4	57	29	17	2	13	12	92	32	27	6	22	19	18	95	53	17
VI	0	0	0	7	4	57	1	0	0	14	6	1	17	2	2	100	20	8
VII	1	0	0	4	22	1	13	12	92	37	22	1	5	11	10	91	38	18
VIII	3	1	33	15	17	4	25	9	36	37	42	9	21	18	14	78	35	34
IX	0	0	0	4	0	0	0	0	0	7	3	43	4	3	75	29	10	3
X	0	0	0	5	1	20	1	1	100	11	8	2	25	5	4	80	23	17
XII	1	1	100	17	5	0	3	3	100	25	9	2	22	6	4	67	60	4
XIV	3	2	67	30	7	0	2	2	100	18	9	1	11	4	4	100	33	8
XVIII	1	1	100	8	11	3	3	3	100	30	7	2	29	3	3	100	27	8
XX	1	1	100	20	4	0	1	1	100	8	12	2	17	2	2	100	13	13
Others	3	1	33	8	37	6	5	4	80	14	32	8	25	3	3	100	10	28
Total	80	38	48	21	301	32	225	160	71	37	391	73	19	277	253	91	47	312

* Treatment with serum

possibly, also, there was a larger percentage of older patients than usual.

Age (tables 2 and 3, chart 1) —The mortality rate increased progressively with the ages of the patients, this being true for patients

both with and without bacteremia. It was also true, in general, of the patients with each type of pneumonia. The incidence of bacteremia in each age group paralleled the mortality through the fifth decade, after which the mortality continued to increase steadily, whereas the incidence of bacteremia showed a relative decline up to the eighth decade and an absolute decline later. This is seen graphically by comparing the heights of the solid and of the adjacent striped bars in chart 1. The incidence of bacteremia in both the fatal and the nonfatal cases was relatively lower in the aged patients (70 years and over) and in adolescent children (from 12 to 19 years) than in the other age groups.

Sex (table 2) —The incidence of bacteremia and the death rates were very similar for males and females.

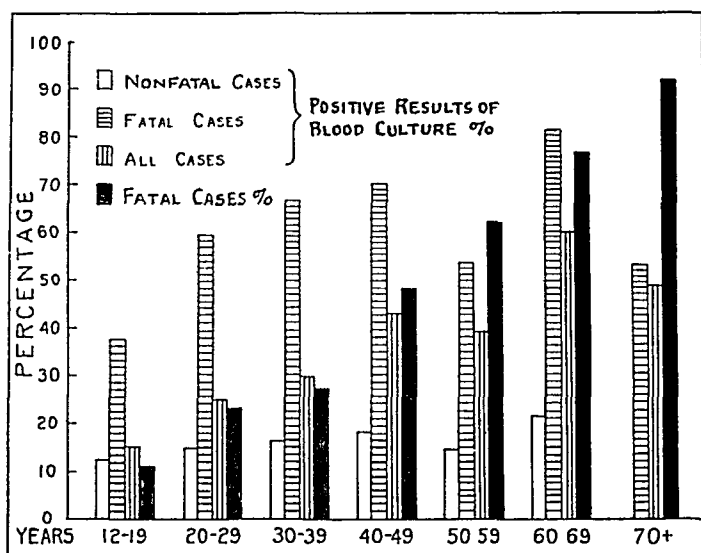


Chart 1—Comparison of the incidence of bacteremia and the mortality for various age groups

Lobar Pneumonia and Bronchopneumonia (table 4) —It was pointed out by Sutliff and Finland⁵ that for all types of pneumococci except type III the mortality in cases of bronchopneumonia is considerably higher than in cases of lobar pneumonia due to the same type of pneumococcus. The greater mortality in the cases of bronchopneumonia (better termed "atypical" pneumonia⁶) was here found in each type, both with and without bacteremia. Bacteremia, however, was less frequent for most types in the cases of atypical pneumonia, indicating

5 Sutliff, W. D., and Finland, M. The Significance of the Newly Classified Types of Pneumococci in Disease. Types IV to XX Inclusive, *J. A. M. A.* **101**: 1289 (Oct. 21) 1933.

6 Cole, R. Acute Pulmonary Infections, in *De Lamar Lectures, 1927-1928*, Baltimore, Williams & Wilkins Company, 1928.

that the high mortality in such cases is due to the frequency with which this kind of pneumonia occurs as a complication or as a terminal event in the course of other serious conditions⁵

Extent of Pulmonary Involvement (table 5) —The death rate was higher in the cases in which the greater amount of lung was involved. This was true regardless of whether or not bacteremia was noted, and also, in a general way, within the different age groups. Bacteremia was considerably more frequent in the cases in which two or more lobes

TABLE 4—*Incidence of Bacteremia and Mortality in Cases of Lobar Pneumonia and in Bronchopneumonia*

Type of Pneumococcus Treatment with Serum		Lobar Pneumonia								Bronchopneumonia							
		Blood Cultures								Blood Cultures							
		Positive				Negative				Positive				Negative			
		No of Cases	Fatal Cases	Fatal Cases, %	Positive, %	No of Cases	Fatal Cases	Fatal Cases, %	Positive, %	No of Cases	Fatal Cases	Fatal Cases, %	Positive, %	No of Cases	Fatal Cases	Fatal Cases, %	Positive, %
I	S	69	25	36	36	123	15	12	0					0			
I		114	95	83	45	137	32	23	9	9	100	64	5	5		100	
II	S	31	20	65	40	47	6	13	0					0	0		
II		61	46	75	58	42	11	26	1	1	100	25	3	3	3	100	
III		100	98	98	47	115	43	37	18	18	100	38	29	15	52		
IV		11	10	91	41	16	3	19	4	4	100	44	5	3	60		
V		32	27	84	38	52	12	23	7	7	100	44	9	5	56		
VI		2	2	100	11	16	7	44	1	0	0	17	5	3	60		
VII	S	1	0	0	11	8	0	0	1	1	100	100	0	0			
VII		20	18	90	29	49	5	10	3	3	100	38	5	4	80		
VIII		38	17	45	38	62	11	18	8	7	87	21	31	18	58		
IX		3	2	67	18	14	3	21	1	1	100	13	7	3	43		
X		3	2	67	15	17	5	29	3	3	100	19	13	9	69		
XII		8	6	75	32	17	3	18	2	2	100	67	1	0	0		
XIV		9	8	89	37	15	2	13	0			0	9	6	67		
XVIII		4	4	100	18	18	5	28	3	3	100	27	8	6	75		
XX		0			0	16	3	19	4	4	100	24	13	5	38		
Others		7	5	71	10	64	14	22	4	3	75	11	33	17	51		
Serum treat- ment		101	45	44.5	35	178	21	11.8	1	1	100.0		0	0			
No serum treatment		412	340	85.2	39	650	159	24.4	68	67	98.5	28	176	102	58.0		
Total		513	385	75.0	38	828	180	21.7	69	66	95.0	28	176	102	58.0		

were involved than in the cases in which the disease was limited to a single lobe. When three lobes were involved the incidence of bacteremia was somewhat higher than when two lobes were involved. For any given amount of involvement there was a higher incidence of bacteremia in the older age groups, but this difference was especially marked in the cases in which a single lobe was affected. Involvement of two or three lobes was more frequent in the older age groups (table 6).

Alcoholism (table 7) —There was little difference in the incidence of bacteremia or in the death rates among those patients who said they

had not used alcohol and those who were habitual drinkers, including even those who were acutely intoxicated from alcohol or had delirium tremens at the time of admission to the hospital. The younger alcoholic addicts, however, showed a higher incidence of bacteremia and a higher

TABLE 5—Incidence of Bacteremia and Mortality in Relation to the Number of Lobes of the Lungs Involved

Age Group	Treatment*	Blood Cultures															
		Positive				Negative				Positive				Negative			
		No of Cases	Fatal Cases	Fatal Cases, %	Positive, %	No of Cases	Fatal Cases	Fatal Cases, %	No of Cases	Fatal Cases	Fatal Cases, %	Positive, %	No of Cases	Fatal Cases	Fatal Cases, %		
One Lobe Involved								Two Lobes Involved									
12-29	Serum	16	2	13	19	68	1	1	11	3	27	52	10	2	20		
	No serum	16	6	38	11	132	9	7	18	13	72	33	36	7	19		
30-49	Serum	18	6	33	24	56	3	5	14	6	43	56	11	5	45		
	No serum	60	41	68	26	173	26	15	48	39	81	40	72	16	22		
50 and over	Serum	9	6	67	37	15	5	33	8	5	63	62	5	1	20		
	No serum	87	79	91	49	90	31	34	70	67	96	55	58	36	62		
All ages	Serum	43	14	33	24	139	9	6	33	14	42	56	26	8	31		
	No serum	163	126	77	29	395	66	17	136	119	87	45	166	59	36		
Three Lobes Involved														Four or Five Lobes Involved			
12-29	Serum	4	2	50	57	3	0	0	1	1	100	33	2	0	0		
	No serum	5	3	60	22	18	3	17	3	2	67	30	7	3	43		
30-49	Serum	12	8	67	75	4	0	0	3	3	100	75	1	1	100		
	No serum	42	33	78	60	28	4	14	8	6	75	57	6	4	67		
50 and over	Serum	4	2	50	67	2	2	100	1	1	100	50	1	1	100		
	No serum	45	41	91	65	24	14	58	10	10	100	62	6	6	100		
All ages	Serum	20	12	60	69	9	2	22	5	5	100	56	4	2	50		
	No serum	92	77	84	57	70	21	30	21	18	86	52	19	13	68		

* Types I, II and VII serums were used

TABLE 6—Extent of the Pulmonary Lesion in Different Age Groups

Number of Lobes Involved	12 to 29 Years		30 to 49 Years		50 Years or More	
	No of Cases	Incidence, %	No of Cases	Incidence, %	No of Cases	Incidence, %
1	232	66.3	307	55.2	201	46.2
2	75	21.4	145	26.1	141	32.4
3	30	8.6	86	15.5	75	17.2
4 or 5	13	3.7	18	3.2	18	4.1
Total	350	100.0	556	100.0	435	100.0

mortality than the abstainers in the same age group, but there was only a small number of such young imbibers. Only 9 per cent of all the alcoholic patients were less than 30 years of age, as compared with 32 per cent of the abstainers.

Preexisting Systemic Diseases and Other Complicating Conditions (table 8).—There was a significantly greater incidence of bacteremia

TABLE 7—Influence of Alcoholism on Incidence of Bacteremia and on Death Rates

Age Group	Treatment	Blood Cultures															
		Positive				Negative				Positive				Negative			
		No of Cases	Fatal Cases	Fatal Cases, %	Positive, %	No of Cases	Fatal Cases	Fatal Cases, %	Positive, %	No of Cases	Fatal Cases	Fatal Cases, %	Positive, %	No of Cases	Fatal Cases	Fatal Cases, %	
Abstainers and Infrequent Drinkers								Moderate Chronic Drinkers									
12-29	Serum	22	6	27	26	62	2	3	2	0	0	29	5	0	0		
	No serum	26	13	50	18	120	15	13	2	2	100	22	7	1	14		
30-49	Serum	26	11	42	40	39	1	3	5	4	80	33	10	3	30		
	No serum	64	47	73	32	134	21	16	23	17	74	32	50	10	20		
50 and over	Serum	8	5	62	38	13	5	39	7	5	71	64	4	1	25		
	No serum	102	95	93	51	100	61	61	22	19	81	42	30	16	53		
All ages	Serum	56	22	39	33	114	8	7	14	9	64	42	19	4	21		
	No serum	192	155	81	35	354	97	27	47	38	81	35	87	27	31		
Acutely Intoxicated and/or with Delirium Tremens																	
Alcoholic History Not Determined																	
12-29	Serum	2	0	0	40	3	0	0	6	2	33	32	13	1	8		
	No serum	3	3	100	38	5	1	20	17	12	71	17	85	12	14		
30-49	Serum	6	3	50	38	10	1	10	11	6	54	46	13	4	31		
	No serum	32	26	81	48	35	8	23	58	46	79	37	100	25	25		
50 and over	Serum	3	2	67	43	4	1	25	4	2	50	67	2	2	100		
	No serum	19	18	95	43	25	8	32	112	107	95	45	135	83	61		
All ages	Serum	11	5	45	39	17	2	12	21	10	48	43	28	7	25		
	No serum	54	47	87	46	65	17	26	187	165	88	37	320	120	38		

TABLE 8—Effect of Preexisting Complicating Conditions and Systemic Diseases on the Incidence of Bacteremia and on the Mortality

Complicating Condition	Positive Blood Cultures						Negative Blood Cultures					
	Serum Treatment			No Serum Treatment			Positive Blood Cultures, %			Serum Treatment		
	Fatal Cases, %			Fatal Cases, %			%			Fatal Cases, %		
	No of Cases	Fatal Cases	Fatal Cases, %	No of Cases	Fatal Cases	Fatal Cases, %	Serum Treatment	No Serum Treatment	%	No of Cases	Fatal Cases	Fatal Cases, %
Cardiac disease	7	7	100	89	85	96	54	50	6	2	33	89
Pregnancy and the puerperium	7	1	14	11	8	73	54	48	6	1	17	12
Delirium tremens	7	2	29	20	20	100	70	58	3	1	33	18
Postoperative	1	0	0	10	7	70	100	36				18
Cerebral accident				9	9	100		47				10
Carcinoma				9	9	100		56				7
Nephritis and uremia	1	1	100	6	6	100	100	60				4
Leukemia and pernicious anemia				6	5	83		86				1
Tuberculosis (pulmonary)				7	5	71	0	50	1	1	100	7
Asthma (bronchial)	1	0	0	5	4	80	20	31	4	1	25	11
Cirrhosis of liver	1	1	100	4	4	100	100	57				3
Diabetes				5	5	100		38				8
Diabetic coma				1	1	100		17				5
Acute infectious diseases (other than pneumococci)				3	3	100		18				14
Miscellaneous (trauma, morphine addiction, neuritis, embolus, epilepsy, scurvy, ulcer, hemachromatosis, bronchiectasis, sickle cell anemia, gangrene, decubitus, iodine poisoning, periarteritis nodosa, burns)	2	2	100	10	8	80	50	29	2	1	50	25
With previous disease	27	14	52	195	179	92	55	46	22	7	32	232
Without complicating disease	75	32	43	285	226	79	32	32	156	14	9	594

TABLE 9—*Relation of the Leukocyte Count to Incidence of Bacteremia and to Mortality*

Leukocyte* Count, Thousands	Blood Cultures						
	Positive				Negative		
	Number of Cases	Fatal Cases	Fatal Cases, %	Total Cases, %	Number of Cases	Fatal Cases	Fatal Cases, %
Less than 5	33	32	97	69	15	8	53
5 to 9	58	55	95	40	87	35	40
10 to 14	108	87	81	33	223	45	20
15 to 24	160	106	66	31	364	93	26
25 to 34	57	32	56	33	113	26	23
35 and over	27	22	82	40	41	12	29
Not made	139	117	84	46	161	63	39
Total	582	451	78	37	1,004	282	28

* The mean of the counts taken during the acute febrile period of pneumonia was usually taken. If the fluctuations were wide, the highest or lowest count alone was included when that seemed more significant than the mean.

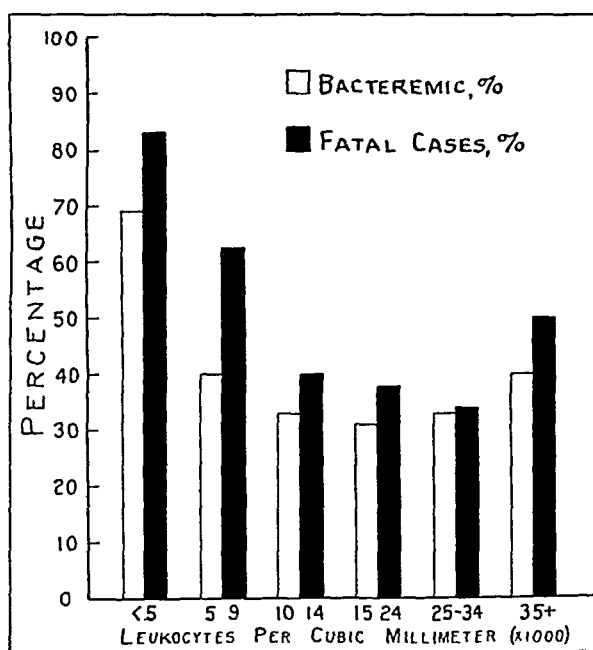


Chart 2—Comparison of the incidence of bacteremia and the mortality for various levels of the leukocyte count

in the cases of pneumonia which occurred in the course of other serious conditions or diseases (so-called secondary pneumonia) than in the cases of primary pneumonia. The death rate in the cases of secondary pneumonia was higher both when positive and when negative blood cultures were obtained, but the difference was most striking in the latter cases.

The Leukocyte Count (table 9 and chart 2) —The differences in the mortality rate at different leukocyte levels varied in the same manner as the incidence of bacteremia. Bacteremia was most frequent in the cases in which the leukocyte count was below 10,000. It was higher

in the cases in which the count was 35,000 or more than in those in which it was between 10,000 and 34,000. The mortality in all the cases corresponded to the incidence of bacteremia, except in the cases in which the count was less than 10,000, in which there was a relatively higher death rate. The lower counts were somewhat more frequent in the cases of bacteremia.

Postpneumonic Complications (table 10)—Bacteremia was more than twice as frequent in the cases in which there were postpneumonic

TABLE 10—*Relation of Bacteremia to the Incidence and Mortality of Post-pneumonic Complications*

	Blood Cultures														
	Positive						Negative								
	Serum Treatment			No Serum Treatment			Total Cases, %			Serum Treatment			No Serum Treatment		
	Fatal Cases, %			Fatal Cases, %			Fatal Cases, %			Fatal Cases, %			Fatal Cases, %		
	No of Cases	Fatal Cases	Fatal Cases, %	No of Cases	Fatal Cases	Fatal Cases, %	Serum Treat ment	No Serum Treatment	No of Cases	Fatal Cases	Fatal Cases, %	No of Cases	Fatal Cases	Fatal Cases, %	
Empyema	16	5	31	61	55	90	73	65	6	2	33	33	16	49	
Sterile pleural effusion	5	2	60	8	4	50	36	26	9	1	11	23	3	13	
Pulmonary abscess	2	2	100	24	24	100	50	63	2	2	100	14	11	79	
Pericarditis				21	21	100	0	78	1	1	100	6	6	100	
Endocarditis	3	3	100	10	10	100	100	83				3	3	100	
Peritonitis				1	1	100		100							
Meningitis	2	2	100	16	16	100	100	94				1	1	100	
Parotitis	1	0	0	1	1	100	50	50	1	1	100	1	0	0	
Arthritis	1	0	0	4	3	75	100	100							
Subcutaneous abscess	2	0	0	3	2	67	100	60				3	1	50	
Thrombophlebitis	1	0	0	3	2	67	50	60	1	0	0	3	0	0	
Otitis media				3	3	100	0	25	3	0	0	9	3	33	
Conjunctivitis				2	1	50		100							
Streptococcal infection	4	2	50	1	0	0	100	11				8	5	63	
Relapse				1	0	0		33				2	0	0	
With complications*	33	13	39	126	113	90	61	56	21	5	24	98	41	42	
Without complications	69	33	48	354	292	82	31	33	157	16	10	728	220	30	
With complications, %	32			26					12			12			

* Cases of multiple complications are included with each of the complications but only once in the totals.

complications as in those in which there were none. Conversely, the complications were more than twice as frequent in the cases of bacteremia as in the cases in which bacteremia was not noted. The death rate in the cases in which there were postpneumonic complications was higher than in the cases in which pneumonia terminated without such complications, except for the cases of bacteremia in which serum treatment was given. The situation was different in the cases in which the pleural effusion was sterile, the incidence of bacteremia and the death rates in these cases being similar to those in the cases in which there were no "septic" complications.

TABLE 11—*Duration of the Acute Illness*

	Duration of the Acute Illness, Days													Day of Onset or Termination			
	1	2	3	4	5	6	7	8	9	10	11	12	13 to 15	16 to 20	20 and Over	Indefinite	Total
Positive blood cultures																	
Serum																	
Number of cases	0	1	3	13	14	15	12	10	5	3	5	2	5	1	4	9	102
Fatal cases		1	1	2	8	5	3	8	3	2	3	1	3	0	4	2	46
Fatal cases, %		100	33	15	57	33	25	80	60	67	60	50	60	0	100	22	45
No serum																	
Number of cases	2	5	9	25	21	37	51	42	43	39	27	18	22	19	19	96	480
Fatal cases	2	4	6	22	19	26	45	33	35	30	25	15	22	17	18	86	405
Fatal cases, %	100	80	67	88	91	70	88	79	73	77	93	83	100	89	95	90	84
Negative blood cultures																	
Serum																	
Number of cases	1	2	12	39	43	30	18	12	5	1	3	2	7	0	2	1	178
Fatal cases	0	0	1	1	3	1	5	3	2	0	1	0	2		2	0	21
Fatal cases, %	0	0	8	3	7	3	28	25	40	0	33	0	29		100	0	12
No serum																	
Number of cases	0	9	20	41	67	71	89	97	83	42	36	27	49	25	23	147	826
Fatal cases		4	4	16	12	15	23	17	18	8	13	10	14	9	19	79	261
Fatal cases, %		44	20	39	18	21	26	18	22	19	36	37	29	36	83	54	32
Serum treatment																	
Number of cases	1	3	15	52	57	45	30	22	10	4	8	4	12	1	6	10	250
Fatal cases	2	14	29	66	88	108	140	139	131	81	63	45	71	44	42	243	1,306
No serum treatment																	
Number of cases	2	14	29	66	88	108	140	139	131	81	63	45	71	44	42	243	1,306
Total																	
Number of cases	3	17	44	118	145	153	170	161	141	85	71	49	83	45	48	253	1,586
Fatal cases																	

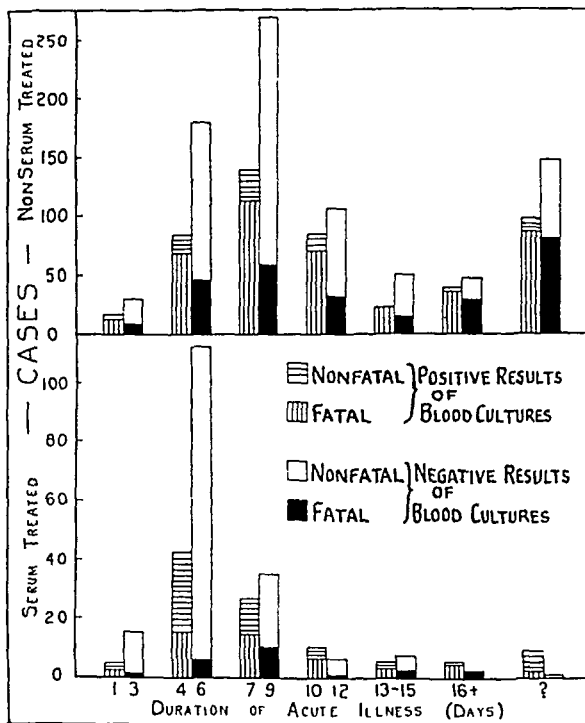


Chart 3—Comparison of the duration of the acute illness, the mortality, the incidence of bacteremia and the type of treatment for various age groups. The height of the columns represents the number of cases.

Duration of the Acute Disease (table 11 and chart 3) —In the cases in which no specific serum was given the termination of the acute disease by crisis, lysis or death occurred most frequently between the seventh and the ninth day. This was true regardless of the presence of bacteremia. In the cases in which serum was administered recovery was usually between the fourth and the sixth day, regardless of whether

positive or negative blood cultures were obtained. Fatalities in the cases in which specific treatment for bacteremia was given occurred with equal frequency between the fourth and the sixth day and between the seventh and the ninth day, whereas the fatalities in the cases in which bacteremia was not present and in which serum was administered were most frequent during the latter interval. In the cases of pneumonia either with or without bacteremia in which serum was not given the death rates were higher in cases in which the disease terminated after the tenth day than in those in which the acute disease ended earlier. In the cases in which serum was given the mortality was higher when the disease ended after the seventh day when the blood

TABLE 12—*Incidence of Bacteremia and Mortality on Each Day of Illness*^{*}

Day of Illness	Serum Treatment Blood Cultures							No Serum Treatment Blood Cultures						
	Positive			Positive, %	Negative			Positive			Positive, %	Negative		
	No of Cases	Fatal Cases	Fatal Cases, %		No of Cases	Fatal Cases	Fatal Cases, %	No of Cases	Fatal Cases	Fatal Cases, %		No of Cases	Fatal Cases	Fatal Cases, %
1 and 2	19	6	31	34	37	5	14	22	12	54	19	92	31	33
3	32	14	44	28	82	5	6	33	23	70	22	118	26	22
4	23	10	43	24	74	11	15	57	42	74	32	118	21	18
5	21	9	43	24	67	12	18	54	40	74	28	141	29	25
6	11	6	54	19	45	10	22	47	35	74	30	147	40	27
7	13	10	77	31	28	7	25	58	46	78	37	100	21	21
8	7	3	43	33	14	4	29	55	46	83	37	94	21	22
9	4	2	50	25	12	4	33	39	36	92	42	48	12	25
10	2	1	50	20	8	5	63	24	22	91	35	45	14	31
After 10	11	7	64	41	16	6	38	46	40	87	37	80	31	39
Not determined	2	2	100	50	2	2	100	39	36	92	40	59	30	41

* Blood cultures taken after recovery by crisis or lysis are not included

cultures were positive or after the sixth day when the blood cultures were sterile.

Blood Cultures on Various Days of Illness (table 12).—For the cases in which positive blood cultures were obtained there was a higher mortality than for the cases in which negative cultures were obtained, irrespective of the day when the cultures were taken. The incidence of bacteremia when serum treatment was withheld increased moderately as the disease advanced, and this was accompanied with some increase in the death rate, particularly in the cases of bacteremia.

Variations in the Results of Blood Cultures in the Same Case (table 13).—Sterilization of the blood stream without apparent improvement of the acute symptoms or in spite of a progression of the pulmonary lesion occurred more frequently after serum therapy was given than in cases in which no serum was administered. The mortality in such

cases, both with and without serum treatment, was lower than for the entire group of cases of pneumonia with bacteremia (table 1), when serum was not given, however, the mortality was still high. The explanation for the lack of adequate improvement and for the occasional initial appearance of a positive blood culture after the beginning of serum therapy may rest on the inadequacy or lateness of the treatment.⁷ The death rate in the cases in which positive blood cultures were

TABLE 13—*Outcome in Cases in Which Both Positive and Negative Blood Cultures Were Obtained*

		Serum Treatment	No Serum Treatment	Total Number of Cases
Positive cultures, followed by negative cultures during acute illness or at autopsy	Number of cases	48	43	91
	Fatal cases	9	26	35
	Fatal cases, %	19	60	38
Negative cultures, followed by positive cultures during life or at autopsy	Number of cases	4	47	51
	Fatal cases	3	40	43
	Fatal cases, %	75	85	84

TABLE 14—*Results of Cultures of Heart Blood at Autopsy*

Cultures Made During Life	Total Number of Cases	Postmortem Blood Cultures					
		No Serum Treatment			Serum Treatment		
		Positive	Negative	Positive, %	Positive	Negative	Positive, %
None	209	114	94	55	1	0	100
Positive	91	62	18	78	8	3	73
Negative	55	18	31	37	1	5	17
Positive and later negative	4	1	1	50	0	2	0
Negative and later positive	10	6	2	75	1	1	50
Negative, positive and later negative	1	0	0		1	0	0
Successively positive, negative, positive and negative	3	0	1	0	0	2	0
Positive for hemolytic streptococcus*	8						
Positive for Friedlander's bacillus†	1						
Total	382	201	147	58	12	13	48

* Antemortem cultures 5 negative and 2 that were first negative and then positive (for pneumococcus). In 1 case no antemortem culture was made.
† Positive for Friedlander's bacillus during life.

obtained after the cultures had been sterile was the same as for all the cases of bacteremia.

Postmortem Blood Cultures (table 14).—The incidence of positive cultures of heart blood, made usually from two to eighteen hours post mortem, was similar to that found in all the fatal cases (table 1). Positive cultures were obtained for heart blood in over a third of the

7 Finland, M., and Dowling, H. F. The Dose of Antibody Effective in the Treatment of Pneumococcus Type II Pneumonia, *Am J M Sc* **191** 658 (May) 1936. Finland, M. Adequate Dosage in the Specific Serum Treatment of Pneumococcus Type I Pneumonia, *ibid* **192** 849 (Dec) 1936.

cases in which such cultures were made after sterile cultures had been obtained during life

Bacteremia and Multiple Types of Pneumococci (table 15) —Positive blood cultures may be of great assistance in determining the etiologically significant organism in cases of pneumonia with "mixed infections" Type I pneumococcus invaded the blood stream in all 9 cases of bacteremia in which this type occurred along with other types of pneumococci Type III pneumococci, on the other hand, invaded the blood in only 6 of the 9 cases of bacteremia in which this type and others were involved Type X occurred in 3 cases and type XX in 2 cases in which other types of pneumococci were cultured from the

TABLE 15—*Multiple Types of Pneumococcus in Cases of Bacteremia*

Case*	Termination†	Type of Pneumococcus				
		Sputum	Blood Culture During Life	Pleural Fluid	Lung (Autopsy)	Heart Blood (Autopsy)
1	D	I, III	I			
2	D	X	I		I	0
3	D	I, III	I, III		I, III	
4	D	XXX	I		I	0
5	D	VI			I	I
6	D	I, X	I			
7	D	XX				I
8	D	I, XXIV	I		I	I
9	D	I, II	I		I	I
10	D	XX	II			
11	D	III, VIII	III			III
12	D	III, XXI	III			
13	D	III	III		III, XXIV	III
14	D	III, XXIII	III			
15	D	VIII	III			
16	D		IV		IV, XIII	IV
17	D	V		V	V, X	V
18	R	III, XI	XI			
19	D	III, XIV	XIV		XIV	XIV
20	R	X, XXXI	XXV			

* In cases 1 to 3 serum treatment was given

† R indicates recovered, D, died

blood It cannot always be determined, however, whether such findings are the result only of the lack of invasiveness of certain types or whether they indicate that these types are not related to the pulmonary infection Other methods may be invoked and may help in such cases or in cases in which sterile cultures are obtained² In only 1 of our 20 cases were two types identified in the blood In this case type I and type III pneumococci were found It is possible and likely that other instances of invasion of the blood stream with more than one type of pneumococcus have been missed

Quantitative Blood Cultures —Fluctuations from day to day between positive and negative blood cultures for the same patient, even with specific serum therapy, have already been noted Such variation may depend, in general, on the degree of bacteremia, that is, the number of pneumococci per cubic centimeter of blood, or possibly on the methods

used in taking the cultures. In a number of cases, however, the blood exhibited a remarkable ability to sterilize itself even without therapy and occasionally even after a heavy invasion. For the bacteremic patients who recovered the colony count was usually below 10 per cubic centimeter of blood⁸. The prognosis was usually unfavorable when the number of colonies increased in successive blood cultures,⁹ but this was not invariably true, as will be seen from some of the cases to be cited here.

The heaviest invasion encountered in a fatal case was estimated at 35,000 colonies of type II pneumococci per cubic centimeter of blood. This was obtained in a 53 year old patient with cirrhosis of the liver and pneumonia involving two lobes. The largest number of colonies per cubic centimeter grown from the blood of a patient who recovered without serum therapy was 1,700. This was a case of type V pneumonia and will be described herewith. A few instances in which the blood became sterile after heavy invasion and without specific therapy will be noted briefly.

A man aged 62 years with a single lobe of one lung consolidated showed 20 colonies of type I pneumococcus per cubic centimeter of blood on the eighth day of his illness. Daily cultures thereafter showed 70, 200, 80, 50, 12, 29 and 2 colonies per cubic centimeter of blood respectively. The cultures taken from the fifteenth to the nineteenth day, inclusive, were all sterile. The patient died on the twenty-third day of his illness, and the culture of the heart blood at autopsy was sterile.

Recovery occurred in a case of pneumonia due to type I pneumococci with 225 colonies per cubic centimeter of blood. The patient was a man 34 years old who showed acute alcoholic intoxication at the time of his admission to the hospital. Blood cultures showed 60 colonies per cubic centimeter on the fourth day, 225 colonies on the fifth, 21 colonies on the eighth, a positive culture in broth but no growth in the plates on the twelfth day and sterile cultures on the fifteenth, sixteenth and nineteenth days. His convalescence was complicated by septic arthritis due to type I pneumococcus, but eventually he made a complete recovery.

On the fifth day of illness a 32 year old man who showed acute alcoholic intoxication at the time of his admission to the hospital had 250 colonies of type II pneumococcus per cubic centimeter of blood. The entire right lung was consolidated. No specific therapy was given. On the seventh day the pour plates showed 17 colonies per cubic centimeter of blood, and on the ninth day the cultures were sterile and lysis began. The patient had a small empyema and conjunctivitis, from both of which type II pneumococci were cultured. Both these complications cleared rapidly and completely, the former after a single thoracentesis and the latter after local irrigations.

A woman of 27 had pneumonia due to type V pneumococci after a miscarriage. On the second day of the pneumonia a culture showed 50 colonies per cubic

8 Cole, R. Acute Lobar Pneumonia, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1920, vol 1, p 248.

9 Koch, K. R. The Prognostic Value of Repeated Blood Cultures in Pneumococcus Lobar Pneumonia, Am J M Sc 184 364 (Sept) 1932.

centimeter of blood On the third day there were 5 colonies and on the fourth day 1,700 colonies per cubic centimeter of blood On the fourth day dilation and curettage, with removal of retained placental fragments were carried out Blood cultures taken on each of the next two days were sterile Recovery by lysis began on the ninth day and was followed by an uneventful convalescence

A man aged 21 showed 65 colonies of type VII pneumococci per cubic centimeter of blood on the twenty-sixth day of illness Blood culture on the thirty-first day was sterile, but the patient died of empyema two days later

Résumé of the Data Relating to Specific Serum Therapy—During the period covered by this study concentrated specific antipneumococcus serum was used in the treatment in a large proportion of the cases of type I and type II pneumonia The results of this therapy are dealt with in greater detail elsewhere¹⁰ A small number of patients with type VII pneumonia were treated with specific serum during the latter part of this study In the accompanying tables all of these cases in which specific treatment was given and in which blood cultures were made are included and for the most part listed separately, in order to indicate the differences in death rate when compared with the cases in which specific serum treatment was not given It is well to review these findings briefly

The incidence of bacteremia was the same for all the serum-treated patients as for the nonserum-treated patients The survivals after serum therapy included a much larger percentage of the cases of bacteremia than was found for the cases in which recovery was obtained without serum treatment (table 1)

For the cases in which bacteremia was not present, the differences in mortality were equally striking in each of the types in which serum was used A similar difference was noted in the cases of type I pneumonia in which blood culture was positive, but the difference was not nearly as striking in the cases of type II pneumonia (table 1)

The young and the old patients, the bacteremic and the nonbacteremic, all shared in varying degrees in the reduction in mortality from serum therapy (table 3) There are no data available concerning serum therapy in cases of bronchopneumonia (table 4)

In general, the death rates were lower among the serum-treated patients, irrespective of the number of lobes of the lungs involved, both in those with and in those without bacteremia (table 5)

Serum-treated alcoholic patients also showed a lower mortality than nonserum-treated patients with similar alcoholic habits, irrespective of

10 Sutliff, W D, and Finland, M Type I Pneumococcic Infections with Especial Reference to Specific Serum Treatment, *New England J Med* **210** 237 (Feb 1) 1934 Finland, M, and Sutliff, W D The Specific Serum Treatment of Pneumococcus Type II Pneumonia, *J A M A* **100** 560 (Feb 25) 1933 Finland and Dowling⁷

age and the "degree" of alcoholism. This was true for both the bacteremic and the nonbacteremic patients (table 7).

Patients with significant preexisting systemic diseases likewise showed a lower mortality if treated with serum. The differences in the death rates were similar to those found among patients without these complicating conditions (table 8).

Septic complications occurred with equal frequency among serum-treated and nonserum-treated patients. This was true for both bacteremic and nonbacteremic patients (table 10). Large sterile effusions occurred in a higher percentage of serum-treated (5 per cent) than in untreated patients (3 per cent).

Recovery by crisis or lysis occurred earlier in the serum-treated patients, both bacteremic and nonbacteremic. No striking difference between serum-treated and nonserum-treated patients was observed with regard to the duration of the disease in the fatal cases (table 11, fig 3).

The incidence of bacteremia tended to decline each day for the first six days of the disease among the recipients of serum, whereas among those who were not treated with serum the incidence of positive blood cultures tended to increase each day. After the sixth day the incidence of bacteremia among the serum-treated patients fluctuated from day to day and tended to approach that found among the patients treated without serum. Considering the results of blood cultures taken on different days of the disease up to the sixth day, the mortality was consistently lower among the serum-treated patients, whether the cultures were positive or negative. After the seventh day, however, the mortality was lower only for the patients who showed positive blood cultures (table 12).

The influence of serum in helping to sterilize the blood stream was reflected by the frequency with which positive blood cultures were followed by negative cultures, even when the disease was still in progress (table 13), by the rarity with which positive blood cultures were observed after previous cultures had remained sterile (table 13) and by the somewhat lower percentage of positive cultures of heart blood post mortem for the specifically treated patients (table 14).

It is to be emphasized that the patients listed here as serum-treated include all the patients receiving the homologous type of antibody, irrespective of the amount or the time of its administration. The importance of the dose of antibody and of the day of the disease when it is given are considered in detail elsewhere.⁷

COMMENT

Space does not permit a detailed discussion of all the possible implications and deductions which may be drawn from the data here pre-

sented. It is hoped that these findings will help to answer a number of questions with regard to the significance of bacteremia, which can be answered only after a laborious analysis of a large amount of material in some such manner as was here attempted.

Much of the earlier literature purported to show that pneumonia is always accompanied with bacterial invasion and that the divergent results obtained by different observers may be ascribed to the technics used in making the blood cultures.¹¹ Such a view would necessarily divest of any prognostic significance the finding of pneumococci in the blood of patients with pneumonia. There is considerably better agreement in the more recent literature in this regard, and the differences in the incidence of bacteremia and the mortality, while the figures may possibly vary for different localities or for different years,⁴ are probably more affected by the choice of cases or by the attempts to draw conclusions from a small number of cases. The more recent knowledge concerning the biology of the pneumococcus¹² has tended to standardize methods sufficiently to exclude this as an important factor.

SUMMARY

A series of 1,586 consecutive cases of pneumococcic pneumonia due to pneumococci of types I to XXXII (Cooper) in which blood cultures were made during life and/or at autopsy was analyzed with respect to the incidence of bacteremia and the mortality. The relation of the finding of positive blood cultures to other factors which are known or supposed to influence the prognosis has been considered. The effect of bacteremia on the occurrence of postpneumonic complications and its influence on the duration of the disease also were noted. Cases in which treatment with specific serum was given have been compared with cases in which no serum was given with respect to most of these subjects. The data are presented largely in tables, and the deductions are summarized in the text under the appropriate headings.

11 Prochaska, A. Bakteriologische Blutuntersuchungen bei Pneumonien, *Centralblatt für inn. Med.* **21** 1145, 1900. Rosenow, E. C. Studies in Pneumonia and Pneumococcus Infections, *J. Infect. Dis.* **1** 280, 1904. Kinsey, F. C. Examination of the Blood of Pneumonia Patients for Pneumococci, *J. A. M. A.* **42** 758 (March 19) 1904.

THE BLOOD NITRITE

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Knowledge of the physiology of the nitrites is much confused. This may be attributed in part to the previous lack of a test sufficiently sensitive yet specific for detecting the presence of or measuring extremely minute quantities of nitrite. Very minute doses of nitrite have profound physiologic effects. Although an immense amount of investigation has yielded many significant observations, many enigmas still remain unsolved in this complex field.

Glyceryl trinitrate was discovered by Sobrero¹ in 1847, and the first physiologic studies on nitrites were initiated. Since then the accumulated literature has become enormous, and only a few significant papers can be reviewed here. Early analytic studies² revealed nitrite in many tissues but in some only after the tissues were ground. Liver reduces nitrate to nitrite³. The mechanism of this reduction is not definitely determined, but a vital process is presumably involved because this reduction is completely abolished by one five hundredth molar cyanide. Nitrite is found in human urine only in the presence of *Bacillus coli* infection of the urinary tract and never in normal urine. This fact has been applied as a diagnostic aid⁴.

The pharmacologic effects of nitrite are of two types primarily, relaxation of smooth muscle and, secondarily, other physiologic responses, often due to changes in the circulation. The primary effect

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1 Sobrero, A. *Ann. Chim. (Milan)* **15** 53 (Feb 15) 1847

2 Stepanow, A. *Arch. f. exper. Path. u. Pharmacol.* **47** 411, 1902

3 Bernheim, F., and Dixon, M. *Biochem. J.* **22** 125, 1928

4 Jaeggy, E., and Lanz, W. *Schweiz. med. Wchnschr.* **65** 363, 1935. Mac-hold, K. *Med. Klin.* **30** 1097 (Aug 17) 1934. Merkelbach, O. *Ztschr. f. klin. Med.* **110** 427, 1929. Popper, L., and Weiss, S. *Wien. klin. Wchnschr.* **41** 1081, 1915. Catel, W. *Jahrb. f. Kinderh.* **140** 253, 1933

is most conspicuous on the cells of the smooth muscles of the arterial and arteriolar walls. Secondary effects are observed in secretory organs which are affected by changes in the blood flow. For example, an increased rate of pancreatic secretion follows the administration of nitrite.⁵ Nitrites cause a cessation of peristalsis of the intestines and relaxation of the stomach, with relief of pain due to hypertonicity.⁶ This response has been employed in gastro-intestinal roentgenology to distinguish between spasm and organic constriction. Experiments with isolated strips of intestinal wall^{6b} indicate that nitrite acts directly⁷ on the smooth muscle of the intestines. The effect of nitrite on the smooth muscle of the uterus is less intense but of the same character.⁸ Sodium nitrite has an effect similar to, though of lesser degree than, histamine in increasing gastric secretion.⁹ This effect is due, no doubt, to the vasodilating action of the nitrite.

The administration of nitrite produces a fall in the level of the blood sugar in diabetic as well as in normal subjects, later followed by a rise in the concentration.⁷ This has been explained as due to an increased diffusion of sugar out of the dilated capillaries, but sugar, which reduces nitrite, must itself be oxidized in the process. A fall in blood pressure stimulates the secretion of epinephrine and the consequent liberation of hepatic glycogen.¹⁰ When amyl nitrite is administered to dogs the volume of the liver is reduced.¹¹ Conflicting reports confirm and deny that nitrites affect the rate of oxygen consumption.¹² Hyperpnea, which frequently follows the administration of nitrite, has been attributed to the direct action of the drug on the respiratory center.¹³ There is also evidence¹⁴ that nitrites affect the sensory endings in the carotid sinus and produce reflex hyperpnea.

5 Barlow, O. W. *Am J Physiol* **81** 189 (June) 1927.

6 (a) Beams, A. J. The Effect of Nitrites on Pain and on Motility of the Gastro-Intestinal Tract. I Clinical Study, *Arch Int Med* **49** 270 (Feb.) 1932.

(b) Beams, A. J., and Barlow, O. W. The Effect of Nitrites on the Motility of the Gastro-Intestinal Tract. II Experimental Study, *ibid* **49** 276 (Feb.) 1932.

7 Herzfeld, E., and Kruger, R. *Klin Wchnschr* **8** 1174 (June 18) 1929.

8 Croft, C. R. *Lancet* **2** 166, 1928.

9 Bergman, A. *Prensa med argent* **15** 1526 (May 20) 1929.

10 Tournade, A., and Chabrol. *Compt rend Soc de biol* **93** 934, 1925.

11 Edmunds, C. W. *J Pharmacol & Exper Therap* **18** 155 (Sept.) 1921.

12 (a) Meyers, J. *Arch d mal du cœur* **19** 615, 1926. (b) Weiss, S., and Ellis, L. B. Influence of Sodium Nitrite on the Cardiovascular System and on Renal Activity, *Arch Int Med* **52** 105 (July) 1933.

13 Rosenbluth, E., and Wassermann, S. *Arch f exper Path u Pharmacol* **144** 235, 1929.

14 Dameipolu, D., and Aslan, A. *J de physiol et de path gen* **23** 572 and 606, 1925. Heymans, C., Bouckaert, J. J., and Dautrebande, L. *Compt rend Soc de biol* **106** 1279, 1931.

The use of glyceryl trimtrate in medicine followed Sobrero's discovery in 1847, Guthrie¹⁵ introduced amyl nitrite in 1859, and sodium nitrite was employed clinically for the first time in 1883¹⁶. Arterial dilatation is so general that the soluble nitrites and alkyl nitrates cause a profound reduction of the arterial tension. Insoluble nitrate, as bismuth subnitrate, has been used as a vascular sedative in the treatment of hypertensive arterial disease with encouraging results¹⁷. Sollmann¹⁸ has stated that vasodilatation due to nitrite probably is the result of a direct action on the smooth muscle of the walls of the arterioles, with no significant action on the capillaries and venules, but others¹⁹ have suggested that the capillaries are affected. It has been stated also that the venules are dilated by nitrite²⁰. With active hyperemia induced by arteriolar dilatation an increase in the capillary flow is inevitable. Densham²¹ showed that lactate ion acts as an adjuvant to the vasodilator effect of sodium nitrite. The tone of the vessels also is affected directly by changes in the acid-base balance, but the effect of the lactate ion is specific and is not obtained with hydrochloric acid at a similar hydrogen ion concentration.

A reflex hypertension often follows vasodilatation produced by nitrite²². This vasoconstriction is explained as being due to a secondary stimulation of the vasomotor center resulting from the primary fall in blood pressure and consequent cerebral anemia²³. It is said that the cardiac output is increased somewhat by the administration of nitrites,²⁴ but

15 Guthrie, F. *Quart J Chem Soc* **11** 245, 1859

16 Hay, M. *Practitioner* **30** 180, 1883

17 Stieglitz, E. J. *J Pharmacol & Exper Therap* **32** 23 (Nov) 1927, **34** 407 (Dec) 1928, **46** 343 (Nov) 1932, Bismuth Subnitrate in Treatment of Arterial Hypertension, *J A M A* **95** 842 (Sept 20) 1930, Arterial Hypertension, New York, Paul B. Hoeber, Inc., 1930, Abnormal Arterial Tension, New York National Medical Book Co., 1935. Bruen, C. *J Lab & Clin Med* **18** 138 (Nov) 1932

18 Sollmann, T. *Manual of Pharmacology*, ed 2, Philadelphia, W. B. Saunders Company, 1926, p. 494

19 Deutsch, G., and Liepelt, A. *Deutsches Arch f klin Med* **160** 207, 1928. Leake, C. D., Kammer, A. G., and Hitz, J. B. *J Pharmacol & Exper Therap* **35** 143 (Feb) 1929. Schulman, E., and Marek, J. *Compt rend Soc de biol* **95** 1474, 1926. Carrier, E. B. *Am J Physiol* **61** 528, 1922

20 Payan, L., and Giraud, E. *Compt rend Soc de biol* **93** 351, 1925

21 Densham, B. *J Physiol* **63** 175, 1927

22 Gaucher, M., Lequime, J., and Van Bogaert, A. *Compt rend Soc de biol* **114** 1056, 1933. Dautrebande, L. *Arch internat de pharmacodyn et de therap* **43** 247, 1932. Burgess, A. M. *Ann Int Med* **5** 441, 1931

23 Pilsher, J. D., and Sollmann, T. *J Pharmacol & Exper Therap* **6** 323, 1915

24 Gaisbock, F., and Jarisch, A. *Wien klin Wchnschr* **40** 1540, 1927

this is denied by Weiss and Ellis ^{12b} In this connection it should be mentioned that Weiss and Ellis observed no improvement in renal secretion following the administration of sodium nitrite, in contradistinction to the finding by Mason ²⁵ that the rate of excretion of water by the kidneys is definitely increased secondary to an increased blood flow produced by sodium nitrite, provided the blood pressure is not too markedly lowered ²⁶ It must be emphasized that changes in the renal circulation are dependent not only on the systemic arterial tension but especially on the state of constriction or dilatation of the renal vessels Nitrates have definite diuretic properties ²⁷

A wholly unsolved problem is the question of why the doses required to produce a certain degree of vasodilatation should vary so markedly with the different nitrites and alkyl nitrates One milligram of glyceryl trinitrate produces the same fall in arterial tension as does 40 mg of erythrol tetranitrate, 50 mg of sodium nitrite or 100 mg of amyl nitrite These wide differences cannot be accounted for on the basis of the amount of nitrite ion available It has been assumed, but never proved, that ease of diffusion and cellular penetration are the chief variables The alkyl nitrates act by liberation of the nitrite ion through hydrolysis ²⁸

Tolerance to nitrites is acquired rather easily Crandall and his collaborators ²⁹ demonstrated an acquired tolerance and cross-tolerance between nitrous and nitric acid esters in man The criterion of tolerance in their experiments was an increase in the dose of nitrite necessary to produce headache There is a marked individual variation in the amount of nitrite required to cause headache, but before as well as after tolerance has developed the dose which will cause headache in any one subject is remarkably constant ³⁰ Tolerance to sodium nitrite is produced with difficulty and only after long administration of large doses ³¹ Erythrol tetranitrate, glyceryl trinitrate, ethylene glycol dinitrate, methyl nitrate and amyl nitrite all produce a cross-tolerance ²⁹ This tolerance develops irrespective of the route of administration of the drug The tolerance is to the chemical substance (presumably nitrite ion) and not to the physiologic response, for no cross-tolerance to other vaso-

25 Mason, E C J Lab & Clin Med **9** 529, 1924

26 Loeb, A Deutsches Arch f klin Med **94** 579, 1908

27 Keith, N M, Whelan, M, and Bannick, E G The Action and Excretion of Nitrates, Arch Int Med **46** 797 (Nov) 1930

28 Hay, M Practitioner **30** 422, 1883 Crandall, L A, Jr J Pharmacol & Exper Therap **48** 127, 1933

29 Crandall, L A, Jr, Leake, C D, Loevenhart, A S, and Muehlberger, C W J Pharmacol & Exper Therap **41** 103, 1931

30 Oltman, T Thesis, University of Wisconsin, 1927

31 Myers, H B, and Austin, V T J Pharmacol & Exper Therap **36** 227, 1929

dilators, such as histamine, is acquired. The tolerance, irrespective of the nitrite-forming drug used, lasts for about ten days after withdrawal. Tolerance is acquired most rapidly from those esters most slowly hydrolyzed by alkali.³²

All these pharmacologic studies are of great interest, but they fail to illuminate whether or not nitrites exist as such in the body fluids in the normal state and are concerned with normal physiologic processes and whether the concentration of nitrite in the body fluids is actually increased after the administration of nitrites and/or nitrates. An extremely sensitive, accurate method of analysis is required for the detection and measurement of the nitrite content of the tissue fluids, for the concentration is extraordinarily minute. The development of a more highly sensitive test³³ made possible these studies on the nitrite content of the blood, spinal fluid, saliva, urine and sweat.

METHOD

By using alphanaphthylamine and the disodium salt of betanaphthylamine-6,8 disulfonic acid (known as amino-G acid)—an intense azo dye is produced in the presence of nitrite ions. The "amino-G" salt is substituted for the sulfanilic acid of the Ilosvay test.³⁴ The azo dye is intense violet in acid solution. Nitrite can be detected by this reaction in pure water in dilutions of 1:250,000,000 in the unknown. The test is applicable to quantitative colorimetric determinations because of the relative permanence of the color produced.

Nitrites are especially unstable and active in an acid solution, the liberated nitrous acid is readily destroyed, either by oxidation or by reduction. Certain bacteria destroy nitrite readily. It combines with hemoglobin to form methemoglobin. The nitrite content diminishes rapidly in sterile blood on standing *in vitro*. It is of the utmost importance, therefore, to avoid any destruction of nitrite in the unknown solution prior to the application of the test. When the method is applied to blood the specimen must be preserved so that the nitrite content is unaltered for several hours. It was found that the detectable content of nitrite could be preserved for at least twenty-four hours by mixing the blood with zinc sulfate³³ immediately on withdrawal. A modified Somogyi³⁴ technic for the precipitation of proteins was used throughout these experiments. Details of method and precautions to be observed with the use of this technic were described at length in an earlier paper.³³

The test offers the following advantages over previously reported methods: (a) greater sensitivity, (b) uniformity of color for at least eighteen hours, (c) relatively stable reagents, which keep well, and (d) rapid maximum development of color.

32 Herman, R. F., Leake, C. D., Loevenhart, A. S., and Muehlberger, C. W. *Proc. Am. Soc. Pharmacol. & Exper. Therap.* **27**: 259, 1926. Oltman, T. V., and Crandall, L. A., Jr. *J. Pharmacol. & Exper. Therap.* **41**: 121, 1931.

33 Stieglitz, E. J., and Palmer, A. E. *J. Pharmacol. & Exper. Therap.* **51**: 398, 1934.

34 Ilosvay. *Bull. Chem.* **2**: 347, 1889. Griess, P. *Ber. d. deutsche chem. Gesellsch.* **12**: 423, 1879. Somogyi, M. *J. Biol. Chem.* **86**: 655, 1930.

RESULTS

The test was applied to many samples of blood of normal human beings (table 1), and it was found that nitrites exist in normal blood with an average measured concentration of 0.8 microgram per hundred cubic centimeters. At times a sample from a subject who ordinarily showed some nitrite in the blood was found to give a negative result. In two subjects for whom frequent readings were obtained over a period of two and one-half years, it was noted that negative results were obtained during the warm months of the year. In another patient it was observed that the readings were negative during attacks of gout.

TABLE 1—*Nitrite Content of Normal Blood*

Age	Sex	Arterial Tension	Nitrite Micrograms per 100 Cc
23	M	118/ 80	0.8
72	F	190/ 20	0.7
52	F	170/110	0.6
23	M	115/ 70	1.1
25	M	125/ 85	1.5
25	M	125/ 80	1.2
27	M	125/ 80	0.5
22	M	125/ 75	1.1
22	M	122/ 75	0.9
20	M	120/ 80	0.6
20	M	122/ 75	1.6
38	M	140/ 90	0.6
21	M	124/ 80	1.5
23	F	124/ 85	1.0
24	F	120/ 82	0.8
24	F	120/ 85	0.7
24	F	120/ 80	0.0
34	M	120/ 85	1.1
34	M	118/ 85	1.3
34	M	115/ 85	0.0
35	M	110/ 80	0.5
35	M	114/ 85	0.0
23	M	118/ 75	1.3
23	M	120/ 70	0.8
23	M	135/ 82	0.6
50	M	140/ 85	0.0
Average			0.8

Normal urine contains no nitrite. Known amounts of a standard solution of nitrite were added to acid urine and to alkaline urine. The amount of nitrite which could be measured, as compared with the standard, was decreased in both, with a slightly greater decrease in the alkaline urine. It was observed also that pure solutions of phosphates decreased the amount of detectable nitrite.

The test was applied to saliva collected by means of a special tube fitting over Stensen's duct and was found to yield positive results of a magnitude comparable to that of the blood. Saliva not thus carefully collected is contaminated with bacteria and food particles, and the readings are far higher.

Spinal fluid was obtained from six patients and all six fluids gave negative results.

Tests were carried out on sweat also. Four healthy men were studied. They stayed in a hot room (140 or 150 F) for four periods of ten minutes each, with one half to one hour of rest between periods. The skin was carefully cleansed with soap and water and then with alcohol and ether. The sweat was allowed to flow directly into a test tube containing the "amino G" acid reagent, and the alphanaphthylamine was added later. Each subject had imbibed a total of 1,500 cc of a mixture of orange juice, lemon juice and water. Four successive samples of sweat were collected from each subject (table 2). It will be noted that in the first two subjects there was a progressive decrease in the concentration, whereas in the last two the concentration remained practically constant, at levels paralleling those found in blood.

The test was applied to the blood and spinal fluid of dogs, with consistently negative results. In rabbits both the blood and the urine showed negative results, although the blood gave positive readings after the administration of nitrite.

TABLE 2—*Nitrite Ion in Sweat*

Subject	Nitrite Ion, Micrograms per 100 Cc			
	Period 1	Period 2	Period 3	Period 4
A	15	08	00	00
B	20	10	00	00
C	15	15	13	15
D	16	15	15	14

Thus it is demonstrated that nitrite ion exists in minute but constant amounts in normal human blood, saliva and sweat but that we have been unable to find it in normal spinal fluid and urine. Analyses of the blood, spinal fluid and urine of dogs and rabbits gave negative results for nitrite. The probable sources of the normal blood nitrite are many.

Various foods contain nitrites and/or nitrates. Meats are occasionally preserved with nitrites or nitrates,³⁵ and many legumes and green vegetables contain nitrates. Persons working in glyceryl trinitrate plants or with other nitrates or nitrites absorb enough so that tolerance for the drug develops.³⁶ Certain bacteria, notably *Bacillus coli* and *Bacillus lactis-aerogenes* of the normal intestinal flora, reduce nitrate to nitrite, they do so with greater ease in a semisolid than in a solid.

35 Kolbe, F. *Ztschr f Fleisch- u Milchhyg* **39** 173, 1929. Maze, P, and Maze, P. J. *Compt rend Soc de biol* **115** 15 and 16, 1934.

36 Laws, G. C. The Effects of Nitroglycerin upon Those Who Manufacture It, *J A M A* **31** 793 (Oct 1) 1898. Letts and Rea. *J Am Chem Soc* **105** 1157, 1914. Ebricht, G. E. The Effects of Nitroglycerin on Those Engaged in Its Manufacture, *J A M A* **62** 201 (Jan 17) 1914.

medium and least readily in a liquid medium³⁷ Experiments were carried out with a strain of *B. coli* isolated from the intestinal tract of a human being to determine the ability of this organism to reduce sodium nitrate and bismuth subnitrate It was found that these bacteria reduced these substances and produced relatively large amounts of nitrite The bacteria also reduce nitrite, and, therefore, much of the nitrite formed is thus simultaneously destroyed³⁸ Such reduction of nitrate to nitrite certainly occurs in the bowel when nitrate reaches the colon, with its myriads of *B. coli*

Reduction of tissue nitrates is another source of nitrite Nitrates exist in many tissues of the body² Whelen³⁹ determined the amounts of nitrate and nitrite together as averaging about 1 mg of nitrate nitrogen per gram of tissue, which reveals an ample tissue reserve of nitrate as a potential source of nitrite Iron in the presence of dextrose is a factor in the reduction of tissue nitrate to nitrite⁴⁰ Tests of nitroso-diethylamine for nitrite give a strong positive result Thus, other organic substances may be considered as potential sources of nitrite There are reducing substances in the blood itself which probably act on any nitrate absorbed No appreciable variation in the nitrite in human blood was detected paralleling dietary variation with fasting or with a high intake of meat or vegetables

Nitrite-forming or nitrite-containing drugs increase the nitrite content of the blood Following the administration of sodium nitrite it was possible to demonstrate a rise in the concentration of nitrite in the blood One subject, with an initial arterial tension of 122 systolic and 75 diastolic and a blood nitrite content of 0.86 microgram per hundred cubic centimeters, was given 0.12 Gm of sodium nitrite In one-half hour the arterial tension had dropped to 102 systolic and 65 diastolic, and the nitrite content had increased to 4.5 micrograms per hundred cubic centimeters In one hour the arterial tension was 114 systolic and 70 diastolic, and the nitrite level was slightly reduced to 3.7 micrograms per hundred cubic centimeters In another subject administration of sodium nitrite (0.18 Gm) caused a rise in the blood nitrite which measured from 1 to 3.1 micrograms per hundred cubic centimeters in twenty minutes Experiments in which bismuth subnitrate was administered orally substantiate the hypothesis that ingested nitrate is reduced to nitrite in the lower portion of the intestinal tract by nitrate-reducing

37 Zobell, C. E. *J. Bact.* **24**, 273, 1932

38 (a) Buswell, A. M. *Chemistry of Water and Sewage Treatment*, New York, The Chemical Catalog Company, Inc., 1928, p. 247 (b) Stieglitz, E. J., and Palmer, A. E. *J. Pharmacol. & Exper. Therap.* **56**, 216 (Feb.) 1936

39 Whelen, M. *J. Biol. Chem.* **86**, 189, 1930, *J. Lab. & Clin. Med.* **20**, 755, 1935

40 Baudisch, O. *J. Biol. Chem.* **48**, 489, 1921

bacteria and that the nitrite thus produced is absorbed into the blood stream as such, for the measurable nitrite content of the blood increases correspondingly ^{38b}

The normal detectable nitrite content of the blood, however, is remarkably constant. It is highly probable that there is a continuous formation and simultaneous destruction of nitrite in the blood. Nitrite is rapidly destroyed by blood *in vitro*, and this destruction is due to a number of substances. Protein decreases the amount of nitrite which can be measured, the greater the amount of protein present, the greater the decrease in measurable nitrite. Nitrite and hemoglobin form stable methemoglobin. Precipitation of proteins from egg albumin and solution of nitrite reduces the detectable nitrite in the filtrate to but a fraction of the amount of nitrite originally added. Dialysis of serum or solutions of egg albumin were carried out against pure water, using a pyroxylin membrane, and after dialysis equal amounts of nitrite were added to the fractions. The portion remaining in the sac (undialyzable fraction) showed greater activity in destroying nitrite than did the dialysate. Nitrite is very active chemically and reacts readily with the amine groups of protein.

Dextrose also destroys nitrite. This is demonstrated readily in the test tube. In connection with the effect of sugar on the nitrite readings, the nitrite levels of normal and diabetic subjects were compared. In four diabetic patients, two of whom were receiving insulin and two of whom were not, with concentrations of sugar ranging from 183 to 330 mg per hundred cubic centimeters of blood, no nitrite could be detected in the blood. In one subject with suspected diabetes, with a sugar content of 118 mg per hundred cubic centimeters of blood, without insulin, a positive reading of 0.4 microgram per hundred cubic centimeters of blood was obtained. Further work along this line must be carried out to make these results convincing, these observations are merely suggestive. The administration of nitrates leads to a fall in the level of the blood sugar.⁷

It has long been suspected that normal blood contains thiocyanate ion, which has a powerful destructive action on nitrite. Both thiocyanates and nitrites are vasodilators. In synthetic protein and thiocyanate solutions it was shown that enough thiocyanate remains in the filtrate after protein precipitation to destroy added nitrite. Silver thiocyanate is highly insoluble. Modification of the technic by adding silver acetate immediately to freshly drawn blood gave slightly higher readings than those found in the same blood analyzed in the usual manner. Since minute amounts of thiocyanate will destroy relatively large amounts of nitrite (1 microgram of thiocyanate destroys 10 micrograms of nitrite), and since nitrite is actually found in the blood, this observa-

tion indicates that thiocyanate may exist in normal blood, but only in extremely minute amounts

Comparison of control solutions and solutions containing urea in concentrations equivalent to those in the blood showed no difference in the measurable content of nitrite. Uric acid likewise had no effect. Even the addition of amounts of uric acid such as are observed in the blood in gout showed no diminution of the nitrite content. This is interesting in the light of our not being able to obtain nitrite readings for the blood of one subject with gout during periods of hyperuricacidemia. Epinephrine, however, actively destroys nitrite.

Pure amino-acetic acid, cystine, tyrosine, alanine and leucine were added to standard solutions of nitrite. No appreciable decrease in the concentration of nitrite was observed. Alcohol *in vitro* reduces nitrite. The nitrite content of the blood was found to fall from 0.8 microgram per hundred cubic centimeters to negative findings after several alcoholic drinks.

CONCLUSIONS

With a new sensitive specific test for nitrites studies have been made to determine whether nitrite ion exists in certain normal biologic fluids and what the factors are which control the amounts found in the blood.

It has been shown that nitrite is present in small amounts in the blood, saliva and sweat but not in the spinal fluid or normal urine of man. The concentration of detectable nitrite ion in normal human blood is of the order of magnitude of 1:100,000,000 during the cool months, and frequently none is found in hot weather. The concentration of nitrite in the blood has been shown to increase after the administration of sodium nitrite or bismuth subnitrate.

It has been shown that proteins, sugar, alcohol, phosphates, epinephrine and thiocyanate decrease the amount of measurable nitrite and that blood on standing even a few minutes shows a rapidly decreasing amount of nitrite available for the test. Nitrites are unstable chemically and are readily destroyed either by oxidation or by reduction. Certain bacteria destroy nitrite readily. Because of the rapid disappearance of nitrite from blood and the relative constancy of the level found in freshly drawn blood, one may tentatively assume that there is a constant production and destruction of the nitrite going on in the body. It also seems more than likely that only a fraction of the nitrite which may be in the blood stream is measured. The fact that the normal readings are relatively constant seems to indicate that perhaps an aliquot portion is obtained.

Amino acids, urea and uric acid do not seem to have any influence on the nitrite level of the blood.

The source of the nitrite of the blood may be from administration by any route, absorption of nitrites from the bacterial reduction of food or drug nitrates in the lower portion of the bowel or absorption of nitrates and a subsequent reduction in the blood stream itself or a reduction of nitrates in the tissues. Any of these sources may be foci of a more or less constant production of nitrite, probably in far greater amounts than those shown in the course of these experiments, because of the many factors constantly destroying the nitrite. Nitrite, as nitrous acid, has profound effects in very small amounts on a great many functions of the body directly by its action of relaxing smooth muscle, especially arteriolar muscle, and indirectly by its effects on the blood flow in secretory organs.

The exact physiologic significance of the blood nitrite is uncertain, but it may be that normally it aids in maintaining those functions which are stimulated by the administration of therapeutic doses. Clinical application of nitrite analysis of the blood may reveal some correlation between a disturbed nitrite metabolism and abnormalities of the arterial tension. With a new and far more sensitive test for minute quantities of nitrite, quantitative pharmacologic studies are now made possible.

ABSTRACT OF DISCUSSION

DR ANTON J CARLSON, Chicago. My interest in this work arose from the fact that one is dealing here with a new normal constituent of the internal environment. The nitrites appear to be present in an amount similar to that of some of the vitamins and some of the hormones that have a profound effect in the body economy. The work has been difficult so far. I admire Dr Stieglitz' persistence in contributing to fundamental medical science while making his living in medical practice. I think it is the result partly of heredity and partly of environment. He has opened up a new field here. I do not know whether it is going to be a blind alley or of profound significance, but nitrates given by mouth can apparently be converted to nitrites in sufficient amounts to produce significant physiologic effects.

DR EDWARD J STIEGLITZ, Chicago. This work has been discouraging at times. Nitrite is so easily destroyed, and it is so easy for things to become contaminated. Ordinary tap water as it comes from Lake Michigan contains from a hundred to a thousand times as much nitrite as is found in the blood. Glassware left in the laboratory is contaminated with the fumes of nitrous acid. Glassware must be washed with cleaning solution and rinsed with fresh distilled water within half an hour of its use. The corollary of hormones going around to the frontal lobes did not occur to me, but the work has seemed like the music which goes around and around, very little comes out. Just one little toot has been heard so far, but I am convinced that there is a lot more music in this horn.

EFFECT OF SUNLIGHT ON THE CLINICAL MANIFESTATIONS OF PELLAGRA

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AND

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The influence of the sun's rays on the lesions of pellagra has been a subject of debate for nearly two hundred years. Casal¹ noted a seasonal variation in the incidence of pellagra, with a peak which corresponded to the spring equinox. In Italy one of the common names applied to this disease by the peasants is *mal del sole* (disease of the sun), while certain Italian physicians have described the lesions as due to "sunstroke of the skin"². Many modern clinicians³ have stated

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1 Casal, G, cited by Major, R H. Classic Descriptions of Disease, Springfield, Ill, Charles C Thomas, Publisher, 1932, pp 575-579

2 Sambon, L A. Remarks on Geographical Distribution and Etiology of Pellagra, Brit M J **2** 1272, 1905

3 (a) Sambon² (b) Bouchard, C. Experiences relatives à la production de l'érythème solaire et plus particulièrement de l'érythème pellagrique, Compt rend Soc de biol **29** 253, 1877 (c) Thayer, W S. Note on Pellagra in Maryland, Bull Johns Hopkins Hosp **20** 193, 1909 (d) Wood, E J. The Appearance of Pellagra in the United States, J A M A **53** 274 (July 24) 1909 (e) Randolph, J H. Pellagra and Pellagrins, Arch Int Med **2** 553 (Jan) 1909 (f) Kimbrough, J A. Treatment of Pellagra, South M J **5** 99 (Feb) 1912 (g) Menage, H E. A cursory study of skin manifestations of pellagra with reference to its special importance from a diagnostic standpoint, ibid **5** 88 (Feb) 1912 (h) Niles, G M. The treatment of pellagra, J A M A **62** 285 (Jan 24) 1914 (i) Weston, W. Pellagra in early childhood, Am J Dis Child **7** 124 (Feb) 1914 (j) Voegtlin, C. The treatment of pellagra, J A M A **63** 1094 (Sept 26) 1914 (k) Wilson, W T. Management of pellagra, ibid **65** 1943 (Nov 27) 1915 (l) Swanson, C. The differential diagnosis of the skin manifestation in pellagra from other dermatoses, South M J **9** 117 (Feb) 1916 (m) Bigland, A D. The pellagra outbreak in Egypt. I. Pellagra among Ottoman prisoners of war, Lancet **1** 947, 1920 (n) Klauder, J V, and Winkelman, N W. Pellagra among chronic alcoholic addicts,

(Footnote continued on next page)

their conviction that there is a close relationship between exposure to sunlight and the development of cutaneous lesions in a pellagrin. Various observers⁴ have produced typical cutaneous lesions in pellagrins by exposing normal or recently healed areas of skin to direct sunlight. Gherardini^{3w} demonstrated the effect of the sun by systematically uncovering various parts of the body of each patient. Bouchard,^{3b} Hameau^{3x} and Ormsby^{4a} had their subjects wear fenestrated gloves, Wilson^{3k} had them expose both arms, and we^{3y} have produced typical lesions in subjects by having each expose one arm to direct sunlight. Randolph^{3e} prescribed a sun bath for a Negro with pellagra. After a short period of exposure the patient complained of intense burning of the skin, and he was promptly removed to a dark room, nevertheless, severe dermatitis appeared and was followed by stomatitis, diarrhea and dementia. The patient finally recovered.

The presence of lesions on unexposed portions of the body, such as the elbows, knees, sacrum, scrotum and perineum, has led certain students⁵ of pellagra to deny the influence of sunlight in the production of the dermatitis. Tucker,^{5c} Enright^{5d} and Goldberger and Sebrell^{5f}

J A M A **90** 364 (Feb 4) 1928 (o) Manthos, C. Pellagre d'abord atténuee (pellagroïde), demonstration de la photosensibilisation, Bull Soc franç de dermat et syph **39** 1380, 1932 (p) Gougerot, Burnier, R, and Meyer, J. Pellagre parisienne, *ibid* **38** 847 (June) 1931 (q) Cluver, E N. Pellagra Among the Maize Eating Nations of the Union of South Africa, Brit M J **2** 751, 1929 (r) Bass, C C. Pellagra, M Clin North America **12** 1181 (March) 1929 (s) Hartsock, F M. Radiant Energy Sprue and Pellagra, Mil Surgeon **66** 523 (April) 1930 (t) Smith, J H. The Influence of Solar Rays on Metabolism, Arch Int Med **48** 907 (Nov, pt 2) 1931 (u) Corkill, N L. Pellagra in Sudanese Millet Eaters, Lancet **1** 1387, 1934 (v) Kirby, W L. The Eruption of Pellagra, South Med & Surg **97** 11 (Jan) 1935 (w) Gherardini, cited by Sambon² (x) Hameau, cited by Sambon² (y) Ruffin, J M, and Smith, D T. The Treatment of Pellagra with Certain Preparations of Liver, Am J M Sc **187** 512 (April) 1934 (z) Neusser, E. Die Pellagra in Oesterreich und Rumanien, Vienna, Alfred Holder, 1887.

4 (a) Ormsby, O S. Pellagra, J Cutan Dis **30** 589, 1912 (b) Bouchard^{3b} Randolph^{3e} Wilson^{3k} Gougerot, Burnier and Meyer^{3p} Gherardini^{3w} Hameau^{3x} Ruffin and Smith^{3y}

5 (a) Searcy, G H. An Epidemic of Acute Pellagra, J A M A **49** 37 (July 6) 1907 (b) Warnock, J. Pellagra in Egypt, *ibid* **53** 1664 (Nov 13) 1909 (c) Tucker, B R. Pellagra, with the Analytical Study of Fifty-Five Non-Institutional or Sporadic Cases, *ibid* **56** 246 (Jan 28) 1911 (d) Enright, J I. Pellagra Outbreak in Egypt, Lancet **1** 998, 1920 (e) Crutchfield, E D. Pellagra with Special Reference to the Skin and Mucous Membrane, Arch Dermat & Syph **17** 650 (May) 1928 (f) Goldberger, J. Pellagra, revised by W H Sebrell, in Tice, F. Practice of Medicine, Hagerstown, Md, W F Prior Company, Inc, 1931, vol 9, pp 205-231 (g) Long, J D. Pellagra, J A M A **55** 734 (Aug 27) 1910 (h) Spies, T D. Relationship of Pellagrous Dermatitis to Sunlight, Arch Int Med **56** 920 (Nov) 1935

recognized that an existing lesion can be accentuated by exposure to sunlight, while Spies ^{5h} stated that the cutaneous lesions heal equally well regardless of whether the patient is kept in the dark or exposed to direct sunlight. Bigland ^{3m} and Spies ^{5h} failed to produce lesions in pellagrins by exposing them to sunlight, and Gougerot, Burnier and Meyer,^{3p} Crutchfield,^{5e} Bassi ⁶ and Spies ^{5h} reported that they noted no unfavorable response to ultraviolet radiation.

In an effort to determine which of these conflicting views is correct, an investigation of the subject was begun at Duke Hospital in 1931. It soon became apparent in taking the histories that a majority of patients, when specifically questioned, recalled a prolonged exposure to sunlight shortly before the appearance of the cutaneous lesions. It was noted also that the occurrence of dermatitis was almost invariably followed by constitutional symptoms of varying intensity. In only

TABLE 1—*Relationship of Constitutional Symptoms to the Appearance of Dermatitis in One Hundred and Thirty Cases of Pellagra*

Symptom	Occurrence Before Dermatitis		Occurrence Coincident with or After Dermatitis	
	No. of Cases	Percentage	No. of Cases	Percentage
Sore mouth and tongue	17	13	93	72
Diarrhea	12	9	66	51
Abdominal pain	5	4	16	12
Nausea and vomiting	6	5	25	19
Anorexia	6	5	37	29
Nervousness	6	5	32	25
Mental disturbance	0	0	21	16
Paresthesia	2	2	17	13
Ataxia	0	0	8	6

seventeen of one hundred and thirty consecutive patients with pellagra were the mouth and tongue sore before the appearance of dermatitis. In ninety-three these symptoms were noted coincident with or appeared after the development of cutaneous changes. Diarrhea was present in twelve cases before and in sixty-six after the appearance of cutaneous lesions. The relationship of the most important symptoms to the appearance of dermatitis is shown in table 1.

These findings suggested that the severe constitutional symptoms of pellagra are related in some way to the action of sunlight on the exposed surfaces of the body. Thirty-five patients with clinical pellagra were hospitalized with the object of determining accurately the order of appearance of symptoms after controlled exposure of a portion of the body to the direct rays of the sun. The ordinary hospital diet, with an abundance of fresh red meat, milk, fruit and vegetables, is exactly the diet which Goldberger recommended for the cure of the disease.

TABLE 2—*Standard Basic Diet 1*

	Quan- tity, Gm	Protein, Gm	Fat, Gm	Carbo- hydrate Gm	Miner als, Gm			Vitamins				Calories
					Calcium	Phos- phorus	Iron	A	B	C	D	
Corn meal	92	8.3	2.0	69.0	0.0110	0.1225	0.0006		±			±
Cane syrup	105			89.2					+			+
Flour	111	12.5	1.2	83.4	0.0220	0.1030	0.0010		+			—
Lard	81		81.0									
Rice	25	2.0	0.1	19.6	0.0023	0.0240	0.0002					
Field peas	90	19.2	1.4	54.6	0.0756	0.0760	0.0052	+	++			+
Hominy grits	51	4.3	0.3	10.6	0.0056	0.0734	0.0005	+	++			+
Fat salt pork	60	1.1	51.3	0.0	0.0011	0.0115	0.0001					2,890.0
Cod liver oil, cc	90		90.0			0.0117		++++			++++	810.0
Tomato juice, cc	45	0.4	0.1	2.0	0.0070		0.0002	++	++	++	++	10.3
Ammonium citrate and iron	6						1.0200					
Calcium gluconate	6				0.5580							
Cheese	60	17.4	21.6		0.5586	0.4098	0.0007	++	++			264.0
Total		65.2	249.0	358.40	1.2392	0.8319	1.0285	++++	++++	++++	++++	3,974.3

Therefore, it was necessary to devise a basal diet which was adequate in protein, fat, carbohydrate, calories, minerals and all the vitamins except the pellagra-preventive factor of Goldberger. This diet was called standard basic diet 1 and is detailed in table 2. Although it is not entirely deficient in the pellagra-preventive factor, it produced black tongue when fed to dogs.³³ The last ten patients in this series received standard basic diet 2, which was identical with diet 1 except that tomato juice was replaced by 90 mg. of cevitamic acid.

Patients with moderately severe pellagra were admitted to the hospital, fed the standard basic diet and protected from the direct rays of the sun. The cutaneous lesions usually improved under this regimen. In some cases the constitutional symptoms also subsided, in others they remained the same or became accentuated.

After the preliminary period of observation one hand and forearm and in some cases the corresponding foot and lower portion of the leg were exposed to the direct rays of the sun on from three to five consecutive days. The first exposure was usually for twenty or thirty minutes, and the time was increased by fifteen minutes each day up to a maximum of one hour. Members of the staff and patients with other diseases were used as controls, and in no instance was the exposure severe enough to produce a sunburn. Dermatitis appeared over the exposed areas in thirteen of the thirty-five cases (table 3). Two patients in whom no dermatitis was observed showed constitutional symptoms. No accentuation of the clinical manifestations of pellagra was noted in the remaining twenty patients.

The more important constitutional symptoms which appeared in the fifteen patients after exposure to the direct rays of the sun are shown in tables 4 and 5. The dermatitis which was observed in thirteen of these patients varied from erythema with vesiculation to heavily crusted indurated lesions and was indistinguishable from the cutaneous lesions of spontaneous pellagra (fig. 1).⁷ In eleven instances the lesions were produced on a previously involved area. In eight patients, however, the dermatitis was produced on apparently normal skin which had previously been protected by clothing (table 3). The condition of the tongue became definitely worse in twelve of the fifteen patients (table 4). Diarrhea was precipitated in ten (table 5), nausea in seven, vomiting in six, anorexia in eight and dementia in four. In all the fifteen patients one or more severe constitutional symptoms developed after exposure to direct sunlight. Neither cutaneous lesions nor general symptoms occurred in any of the eleven patients who were reexposed to maximum doses of sunlight following adequate treatment (tables 3 to 5).

7 For other experimentally produced lesions see figures 1 to 3 in article by Ruffin and Smith.³⁷

TABLE 3—*The Occurrence of Dermatitis Following Exposure to Direct Sunlight Data for Thirty-Five Patients in the Hospital Subsisting on a Diet Deficient in the Pellagra-Preventing Factor*

Case	Age	Sex	On Admission	Before Exposure	After Exposure		Exposure After Treatment
					Over Original Lesions	Over New Areas	
1*	66	M	++	+	+	—	—
2*	31	F	+	+	+	—	—
3	9	F	+	+	+	—	—
4	32	F	+	0	0	—	—
5	50	M	+	0	0	—	—
6	21	F	+	0	0	—	—
7	27	F	+++	0	0	—	—
8	27	F	+	0	0	—	—
9*	20	F	+++	0	0	—	—
10	29	F	+	0	0	—	—
11	14	F	+	0	0	—	—
12	30	F	+	0	0	—	—
13	41	F	+	0	0	0	—
14	29	F	++	0	0	0	—
15	23	M	+	0	0	0	0
16	31	F	+	0	0	0	0
17	38	F	+	0	0	0	0
18	55	F	+	0	0	0	0
19	41	F	+	0	0	0	0
20*	45	F	++	0	0	0	0
21†	39	M	+++	0	0	0	0
22†	39	F	++	++	++	0	0
Total 22 cases							
23	25	F	++	++	++++	++++	0
24	35	M	+	0	++	++	0
25†	43	M	+	+	+++	+	0
26	8	M	++	0	+++	+++	0
27	54	M	+++	+	0	+++	0
28	34	F	+	+	++	—	0
29	54	M	++	+	++	—	Died
30†	42	M	++++	++	—	+	Died
31	76	M	+	0	+	++	Died
32	55	F	+	+	++	+++	0
33*	24	F	+++	+	++	—	0
34†	26	F	++++	+	++	0	0
35	42	F	++	±	+++	0	Died
Total 13 cases							

* Negro patient
† Alcoholic patient

TABLE 4—*The Occurrence of Sores Mouth and Tongue After Exposure to Direct Sunlight Data for Fifteen Patients Subsisting on a Diet Deficient in Pellagra-Preventing Substance*

Case	On Admission	Before Exposure	After Exposure	Reexposure Treatment
21†	+++	0	++	0
22†	+	+	++	0
33*	+	+	++	0
23	+	+	++	0
32	+	+	++	0
31	+	+	+++†	Died
30†	+	+	++	Died
29	++	+	++	Died
28	0	0	0	0
27	++	+	+	0
26	+	0	++	0
25†	0	0	+++§	0
24	+	0	0	0
34†	++	0	+++	0
35	+	+	+++	Died

* Negro patient
† Alcoholic patient
‡ Occurred ten days after exposure
§ Scrotal lesions appeared for first time

The following case history illustrates the severe reaction which may follow exposure of a pellagum to sunlight and the harmlessness of such exposure after the deficiency has been corrected by adequate dietary treatment

CASE 32—N C, a white woman aged 55, was admitted to the hospital on April 9, 1934, with a history of recurrent pellagra over a period of twenty years. At the time of entry mild dermatitis was present over the dorsum of each hand, the tongue was red and sore and the patient had little or no appetite and was somewhat constipated. She was given standard basic diet 1 (table 2)

On the second, third, fifth and sixth days after the patient's admission to the hospital the left arm and leg were exposed to direct sunshine for one hour daily

TABLE 5—*The Occurrence of Diarrhea After Exposure to Direct Sunlight Data for Fifteen Patients Subsisting on a Diet Deficient in Pellagra-Preventing Substance*

Case	On Admis- sion	Average No of Stools Three Days Before Exposure	Average No of Stools Three Days After Exposure	Reexposure After Treatment (Average No of Stools Three Days Before Discharge)
21†	10	8	6	6
33*	3	2	4	4
23	1	1	9	1
32	1	1	5	2
31	0	1	1†	Died
30†	2	4	13	Died
29	4	8	11	Died
28	0	0 (Enema)	3	1
27	0	1	1	2
26	0	0 (Enema)	1	1
25†	1	1	1	1
24	0	4	6	4
34†§	1	1	1	1
22†	5	3	9	1
35†	5	7	10	Died
Average	2	3	5	2

* Negro patient

† Alcoholic patient

‡ Diarrhea occurred ten days later (average of five stools)

§ No diarrhea, on the fourth day of exposure severe nausea and vomiting were noted

¶ Violent nausea and almost continuous vomiting occurred after the second day of exposure

There was no involvement of the skin of the leg before the exposure. On the day of the last exposure the dermatitis over the left arm became much worse, and large blisters appeared over the foot. The control, exposed simultaneously, showed no sign of sunburn. By this time the rash on the right arm, which had been protected from the sun, had entirely disappeared. A few days later the tongue became fiery red, and severe diarrhea developed, twenty stools being passed on the fifth day after the last exposure. The patient's general condition became much worse. She was given preparations of liver, as shown in figure 2, but rapidly became worse. She became markedly depressed and eighteen days after the last exposure was disoriented, having definite auditory and visual hallucinations. At this time she was given the regular hospital diet and large doses of an aqueous solution of liver extract⁸. Within four or five days she was greatly improved,

⁸ This extract, known as Valentine's liver extract E 29, was furnished by the Valentine Meat Juice Company, Richmond, Va.

and after ten days she was mentally clear and felt entirely well. She was reexposed to direct sunshine daily for seven days, with no recurrence of symptoms, and was discharged on May 26, all evidences of pellagra having completely disappeared.

Niles^{3h} and Bass^{3r} have reported the development of dermatitis in pellagrins after exposure to heat from a stove. In one of our patients typical pellagra with severe constitutional symptoms followed exposure of the hands to a red hot stove. Another patient presented a similar picture after fighting a brush fire. These observations suggest that the acute manifestations of pellagra in a susceptible subject may be precipitated by exposure to the heat from certain radiant bodies. In the following case the typical cutaneous lesions and associated constitutional symptoms were produced by exposing the hands to the rays of an electric heater. After adequate dietary treatment the patient was reexposed to three times the original amount of heat, without the development of either cutaneous lesions or general symptoms.

CASE 36—W B B, a white man aged 45, was admitted to the hospital on Nov 26, 1935. For six months he had been drinking about 2½ gallons (9.5 liters) of whisky a week, and his diet had been grossly inadequate. He presented a typical picture of pellagra, with minimal cutaneous lesions over the dorsum of each hand, a beefy red tongue and marked anorexia but no diarrhea. Mild peripheral neuritis also was present. He was given a diet deficient in the pellagra-preventing factor.

On the day after his admission to the hospital and again on the following day the patient's left hand was exposed to the rays from an electric coil heater for fifteen minutes at a distance of 36 inches (92 cm). Twenty hours after the first exposure distinct erythema was observed, and vesicles appeared on the morning following the second exposure. The hand of the intern who acted as a control showed no changes. On the day following the last exposure the patient's condition became alarming. The tongue was then fiery red, diarrhea, nausea and vomiting had developed and the patient refused to eat. He was given intravenous injections of dextrose and large amounts of an aqueous solution of liver extract by mouth. For several days there was considerable doubt whether he would survive. The stomatitis began to subside after the second day of this treatment, and by the fourth day the color of the tongue was normal. After five days of dietary treatment the patient's condition was definitely improved, and by the tenth day he was well except for persisting neuritis. One hand was then reexposed daily for five days to the electric coil heater for from fifteen to thirty minutes with no visible local or general effect. The patient was discharged as cured on December 17.

COMMENT

The clinical impression that sunlight is harmful to the pellagrin has been amply confirmed by observations on patients under controlled conditions in this hospital. Thirty-five pellagrins on a deficient diet (table 2) were exposed to the direct rays of the sun. In thirteen dermatitis developed, which was followed promptly by moderate or marked accentuation of the constitutional symptoms. Two other patients

showed similar constitutional reactions but no new cutaneous lesions. The first change usually noted was that the tongue became fiery red, followed by vomiting, diarrhea and, in some instances, dementia. The danger of exposing susceptible pellagrins to the sun's rays cannot be overemphasized, despite Spies'^{5h} recently published conclusions that pellagrins recover equally well whether exposed to sunlight or kept in the dark.

The amount of exposure in each case was not excessive. This is shown by the failure of sunburn to develop in members of the staff and patients with other diseases who were exposed similarly and simultaneously. Furthermore, eleven of the fifteen patients who showed acute symptoms after exposure to sunshine were reexposed after the administration of an abundance of the pellagra-preventing factor, and in no instance did either dermatitis or constitutional manifestations recur. This demonstration of tolerance for direct sunlight is thought essential in determining whether the condition has actually been cured. The suggestion that sunburn may be confused with the dermatitis of pellagra is not in accord with the facts as we have observed them. Contrary to the opinion of Spies,^{5h} experienced physicians in the South have no difficulty in making this distinction (Thayer,^{3c} Menage,^{3b} Swanson,³ⁱ Kirby^{3v} and Wood and Taylor⁹).

The fact that twenty of the thirty-five patients showed nothing to suggest an accentuation of the dermatitis or constitutional symptoms after exposure to sunlight is difficult to explain. However, it was noted that without exception the patients who ate the basic diet with relish promptly recovered and showed only a healthy tan on exposure to sunshine.

In the group of twenty patients in whom no symptomatic relapse was observed, any attempt to test the efficacy of a curative substance would obviously have been futile. This serves to emphasize the importance of producing an accentuation of symptoms as a prerequisite to the evaluation of any curative substance. The failure to take this fact into consideration probably accounts for the voluminous literature on therapy and the numerous unrelated substances which have been reported as specific cures for pellagra.

The cutaneous lesions which were produced experimentally by graded exposures to direct sunlight were apparently identical with the spontaneous lesions, first described by Casal.¹ In addition to this typical dermatitis which appears on the exposed surfaces, patients with pellagra may present (1) seborrhea over the face and neck, (2) hyperkeratoses

9 Wood, E. J. Pellagra, revised by F. R. Taylor, in Christian, H. A., and Mackenzie, J. *Oxford Medicine*, New York, Oxford University Press, 1936, vol. 4, pt. 1, pp. 307-352.

over the bony prominences of the body and (3) lesions about the genitalia. The seborrhea occurs most commonly about the alae nasi but at times over the forehead, face and neck. The orifices of the sebaceous glands are plugged with a dry grayish yellow secretion. This type of lesion has been noted previously in pellagrins¹⁰. An analogous alteration in the sebaceous glands of the rat's tail has been produced by a diet deficient in vitamin G (B_2)^{10c}. There is no relation between the presence of seborrhea and the severity of the disease.

When a pellagrous patient is confined to bed, there is a tendency toward the development of bilateral symmetrical lesions over the bony prominences of the body, such as the elbows, knees, ankles and spinous processes. This lesion apparently is a hyperkeratosis, accompanied with more or less pigmentation. It differs from dermatitis, which occurs on

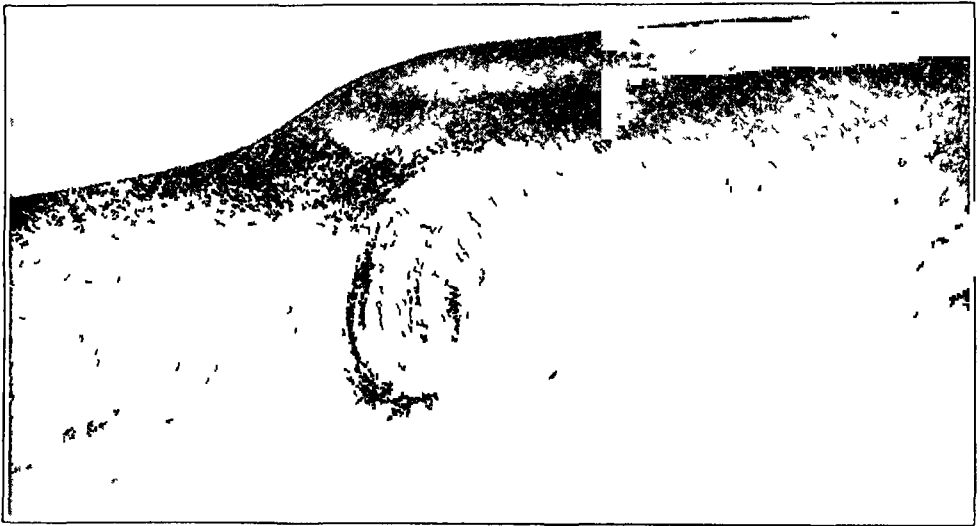


Fig 3—Photograph of hyperkeratosis of the elbow which developed while the patient was in the hospital and receiving an excellent diet. She showed no evidence of pellagra.

the exposed surfaces, by its slow development and by the absence of vesiculation. These lesions rarely, if ever, show crust formation, induration or secondary infection, and their development is not accompanied with an increase in constitutional symptoms. Bilateral symmetrical cutaneous lesions of this type have been frequently observed in both white and Negro patients who were receiving an adequate diet and who showed no evidence of pellagra (fig 3). The cutaneous

10 (a) Castellani, A., and Chalmers, A. J. *A Manual of Tropical Medicine*, ed. 3, London, Bailliere, Tindall & Cox, 1919. (b) Biggam, A. G., and Ghaliboungui, P. Pellagra. Its Clinical Features and Pathology, *Lancet* **2** 1198, 1933. (c) Smith, S. G., and Sprunt, D. H. Pathological Skin Changes in the Tail of the Albino Rat on a Diet Deficient in Vitamin G, *J. Nutrition* **10** 481 (Nov.) 1935. (d) Wood⁹, Bigland^{3m}, Corkill^{3u}, Bass^{3r}.

lesions which Spies⁵¹ "produced" in pellagrins who were confined to the hospital and fed a deficient diet may have been of this type. He recorded no increase in constitutional symptoms accompanying the development of dermatitis. We agree with Bass^{3r} in attributing this type of lesion to mechanical rubbing or pressure over the bony prominences of the body.

The male pellagrin may show lesions on the scrotum or perineum, although perineal lesions are more commonly seen in the female. Perineal lesions are red and macerated and invariably show secondary infection. The vaginal mucosa becomes inflamed in the same manner as the buccal and intestinal mucosa and pours out an irritating secretion. Perineal lesions in the male may be due to constant soiling with foul liquid stools and in the female to this factor supplemented by infected secretions from the vagina. Bass^{3r} stated that the perineal lesions are caused by excoriating secretions and that the occasional lesions found under a pendulous breast are caused by excessive perspiration.

Our observations support the view of Goldberger¹¹ that pellagra is a deficiency disease. The basic deficiency symptoms are easy to recognize as due to "ill health" but difficult to classify. The clinical picture is one of gradually developing lassitude, anorexia, mental torpor, emotional instability, vague digestive symptoms, weakness and dizziness, sometimes with, but more generally without, marked loss of weight. The tongue frequently shows papillary atrophy, especially about the edges. In some cases there is roughness of the skin of the alae nasi and over the forehead and face, and hyperkeratosis may appear in the region of the bony prominences. Although pellagra may be suspected from these symptoms and treated as such, yet we agree with Wood^{3d} and Bass^{3r} that it is hazardous to make a diagnosis of pellagra in the absence of typical dermatitis or a credible history of such a dermatitis on the exposed surfaces of the body.

The reactions which occur after a patient in the deficient state becomes exposed to the sun are dramatic in onset, alarming in severity and not infrequently fatal. The usual story is that a subject who is subsisting on a deficient diet, with many of the vague symptoms already mentioned, though still able to work, exposes himself to the direct rays of the sun early in the spring or summer. Within a few hours a burning and itching sensation is noted over the exposed areas. This is followed in from twenty-four to thirty-six hours by a fiery red erythematous rash. Vesiculation appears, accompanied with induration, dry crusts

11 Goldberger, J. Pellagra. Causation and a Method of Prevention, J. A. M. A. 66 471 (Feb 12) 1916

or secondary infection. The bright red erythema changes to a dull bronze and finally to a deep brown. After the initial erythema the mouth and tongue become red and sore, and diarrhea appears. Dementia may develop without warning and is always an ominous sign.

It should be noted that in two patients with spontaneous pellagra and in one patient under controlled conditions radiant heat from sources other than the sun also produced the clinical picture of the disease.

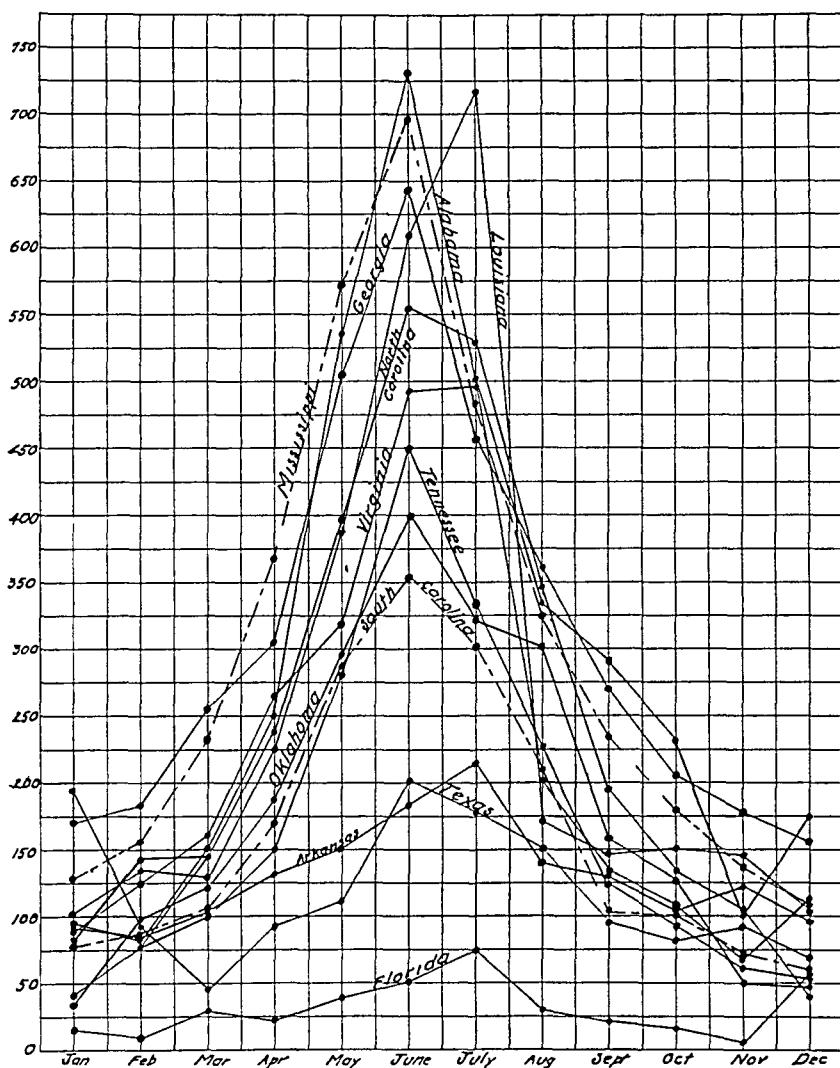


Fig. 4—Chart showing the monthly incidence of pellagra in eleven Southern states over a period of five years (1930 to 1934). In the twelfth state (Arkansas) the monthly mortality is shown. To obtain the actual figures for Mississippi and South Carolina multiply by 10.

The seasonal incidence of pellagra (fig. 4) is apparently conditioned by two factors: the degree of dietary deficiency and the intensity of the solar radiation. In figure 5 the monthly variations in the intensity of sunlight are shown together with the monthly incidence of pellagra.

As Goldberger and his associates¹² have pointed out, there is a gradually accumulating deficiency of accessory food factors during the winter months. When these deficient patients become exposed to the increasing intensity of sunlight during the spring and early summer, the acute symptoms of pellagra appear. When vegetables and milk become more

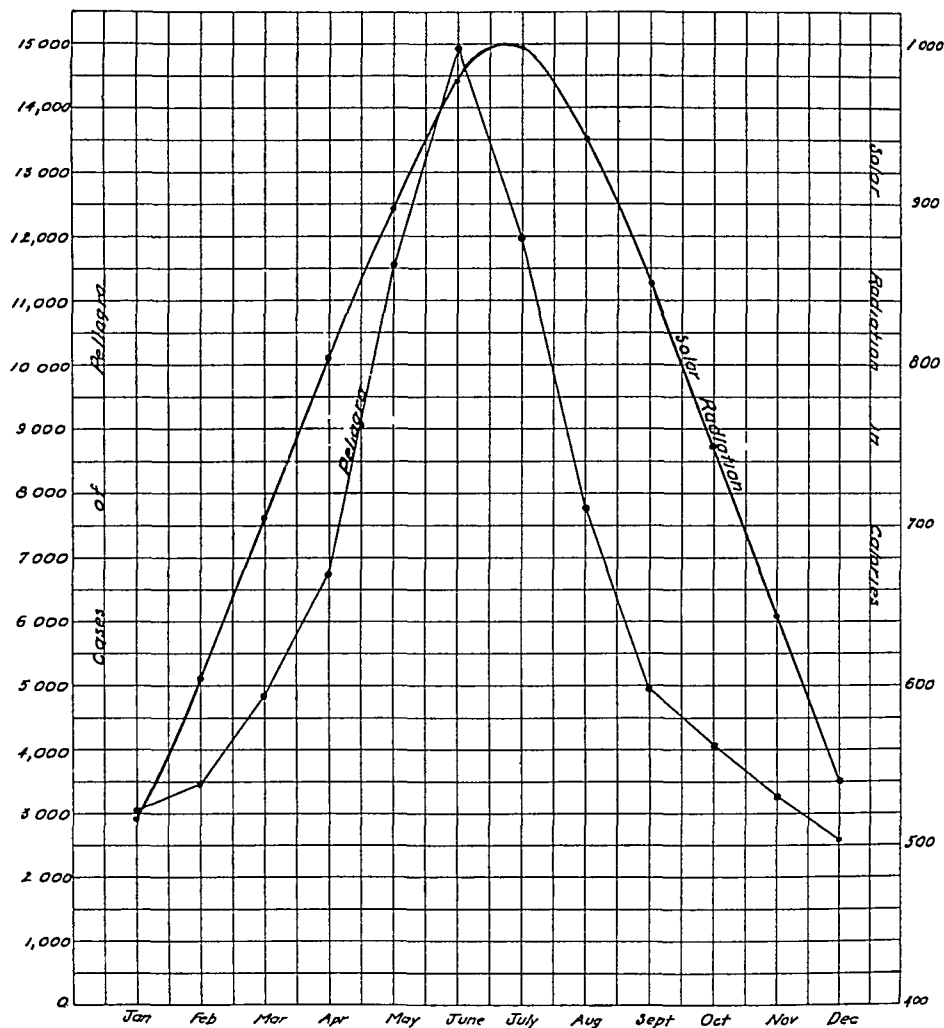


Fig 5—Chart illustrating the relationship of the intensity of the sun's rays to the incidence of pellagra. One curve shows the total monthly incidence of pellagra over a period of five years in the eleven states shown in figure 4. The curve for the total solar radiation is shown in calories per square centimeter per day on a surface at normal incidence at sea level on cloudless days for 33 degrees latitude and was calculated for us by Prof Paul Gross, of the department of chemistry of Duke University, from the curves presented by C G Abbot in his book entitled "The Sun" (New York, D Appleton-Century Company, Inc, 1929, p 385, fig 71)

12 Goldberger, J, Wheeler, G A, Sydenstricker, E, and King, W I. A Study of Endemic Pellagra in Some Cotton-Mill Villages of South Carolina, United States Public Health Service, Hygienic Laboratory Bulletin 153, January, 1929

plentiful during the summer, the deficiencies are corrected and the incidence of pellagra falls rapidly, although the sun remains hot during the month of July and August

CONCLUSION

Exposure of a susceptible subject who has been subsisting on a deficient diet to the sun's rays precipitates the acute manifestations of pellagra

Statistical data on the incidence of pellagra were supplied by Dr J C Knox, of the North Carolina State Board of Health, Dr D G Gill, of the Alabama State Board of Health, Dr I C Riggins, of the Virginia State Board of Health, Dr C M Pearce, of the Oklahoma State Board of Health, Dr C D Reece, of the Texas State Board of Health, Dr Butler Toombs, of the Georgia State Board of Health, Dr C L Brown, of the Louisiana State Board of Health, Dr F A Brink, of the Florida State Board of Health, Dr R N Whitfield, of the Mississippi State Board of Health, Dr W C Williams, of the Tennessee State Board of Health, Mrs J B Collie, of the Arkansas State Board of Health, and Dr M B Woodward, of the South Carolina Board of Health

UVEOPAROTITIS

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The syndrome which is variously designated as uveoparotid fever, uveoparotitic paralysis, uveoparotitis and uveoparotid tuberculosis was brought to the attention of clinicians by Heerfordt¹ in 1909. Since then approximately eighty cases have been reported in the literature, of which not more than seven occurred in the United States. The earlier reports appeared largely in the Scandinavian and German journals of ophthalmology and apparently escaped the attention of the general medical practitioner. Credit is due to the English for reviving interest in the syndrome recently, especially through the medium of the review of Garland and Thomson^{2a} published in 1933. Prior to that, and in the period from 1925 to 1931, only four cases had been reported in the United States (Cutler, Jackson, Hamburger and Schaffer³ and Merrill and Oaks⁴). Subsequently, Levin,⁵ Cogan⁶ and Cohen and Rabinowitz⁷ brought the number of cases reported in this country to seven, and additional reports came from Davies,⁸ Rees,⁹ Tait,¹⁰ Garland and Thomson,² Tanner and McCurry,¹¹ and Savin¹² in England, Mohn¹³ in Denmark and Hafeikorn¹⁴ in Germany.

From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital

1 Heerfordt, C F. Ueber eine Febris uveoparotidea subchronica, *Arch f Ophth* **70** 254, 1909

2 (a) Garland, H G, and Thomson, J G. Uveoparotid Tuberculosis, *Quart J Med* **2** 157, 1933. (b) Garland, H G. Uveoparotid Tuberculosis, *Lancet* **2** 743 and 846, 1934

3 Hamburger, L P, and Schaffer, A L. Uveoparotid Fever as a Manifestation of Mikulicz's Syndrome, *Am J Dis Child* **36** 434 (Sept) 1928

4 Merrill, H G, and Oaks, L W. Uveoparotitis, *Am J Ophth* **14** 15, 1931

5 Levin, Paul M. The Neurological Aspects of Uveo-Parotid Fever, *J Nerv & Ment Dis* **81** 176, 1935

6 Cogan, David G. Uveoparotid Fever, *Am J Ophth* **18** 637, 1935

7 Cohen, S J, and Rabinowitz, M A. Uveoparotitis, *J A M A* **105** 496 (Aug 17) 1935

8 Davies, T A L. Uveo-Parotitis Polyneuritica, *Lancet* **2** 746, 1934

9 Rees, W E. Mikulicz' Syndrome in Association with Tuberculosis, *Lancet* **2** 749, 1934

10 Tait, C V B. Uveoparotitis, *Lancet* **2** 748, 1934

11 Tanner, S E, and McCurry, A L. Uveoparotid Tuberculosis, *Brit M J* **2** 1041, 1934

12 Savin, L H. An Analysis of the Signs and Symptoms of Sixty-Six Published Cases of the Uveoparotid Syndrome, *Tr Ophth Soc U Kingdom* **54** 549, 1934

(Footnotes continued on next page)

The extensive reports of Garland and Thomson^{2a} (1933) covering forty-seven cases in the literature and of Savin¹² (1934) analyzing sixty-six cases and the neurologic study of sixty-six cases by Levin⁵ (1935) render superfluous any attempt to review the literature at this time. Accordingly, a summary of the commoner findings will suffice in this discussion.

The syndrome consists of inflammatory lesions of the uveal tract, enlargement of the parotid glands and a chronic low grade fever. Paralysis of cerebrospinal nerves, particularly the facial nerves, occurs frequently.

The majority of patients have been in the second and third decades of life, with a preponderance of females.

Prodromes, which may be present for a few days or for several weeks, include malaise, weakness, lassitude, drowsiness, nausea, vomiting, loss of weight, fever, puffiness of the eyelids, dryness of the mouth, dysphagia, cough, night sweats, pains in the chest and joints and paresthesias. Not infrequently early in the illness there is a patchy, nonelevated erythema, without itching, involving particularly the legs. The eruption is generally of short duration.

Parotitis is a constant finding. It is usually bilateral, only occasionally being unilateral. The gland is hard and not adherent to the skin, and while not painful, it may be tender to pressure. The swelling is usually of a few weeks' duration but may last for months. No suppuration occurs.

Chronic low grade fever is common but is not a constant finding. The temperature may range from the slightest elevation to from 101 to 103 F in some instances. An afternoon elevation is common.

In addition to parotid enlargement, submaxillary and sublingual involvement is common, and lacrimal swelling occurs occasionally. Generalized lymphadenopathy and splenomegaly have been reported. The commonest finding is enlargement of the cervical lymph nodes.

Ocular manifestations are noted in all cases. Uveitis is the most important of the triad of prerequisites for a diagnosis of uveoparotitis. It is often the earliest symptom, and the resulting visual impairment is permanent, in varying degrees of severity. While the onset may be unilateral, with pain and dimness of vision, bilateral uveitis occurs almost invariably. The pupils may become dilated, irregular and fixed, with the tendency to development of posterior synechiae. Fatty deposits are seen on the posterior surface of the cornea. Nodules, definitely identi-

13 Mohn, A. Ein Fall von Febris uveoparotidea (Heerfordt), *Acta ophth* **11** 397, 1933.

14 Haferkorn, M. Aspects of Heerfordt's Syndrome (Uveoparotid Fever), *Monatschr f Kinderh* **63** 161, 1935.

fied as tuberculous, are said to occur in the iris. Less common findings include hemorrhages into the vitreous, optic neuritis, choroidoirititis, keratitis, glaucoma, turbidity of the aqueous and cataract.

Facial palsy of the peripheral type is the commonest neurologic manifestation, occurring in from one third to one half of all cases. It may be bilateral, although more frequently it is unilateral. Whether the palsy results from choking of the nerve by swelling of the parotid gland, which it usually, although not uniformly, follows, is an unsettled question. There was evidence in Mohn's case to place the site of the lesion between the geniculate ganglion and the branching of the chorda tympani, excluding pressure from a swollen parotid gland. Loss of the sense of taste and bilateral deafness of the central type have been reported. Disturbance of the innervation of the uvula and of the vocal cords is rare. Dysphagia and dryness of the mouth are common. Dysarthria has been attributed to dryness of the mouth by some and to muscular weakness following facial palsy by others.

Polydipsia and polyuria have been reported occasionally, with dilute but otherwise essentially normal urine. Levin said he felt that in his case the condition represented true diabetes insipidus.

Involvement of the spinal nerves may be manifested by a diminished tactile sense, reduction or abolition of the tendon reflexes, tenderness over the peripheral nerves, paresthesias and wrist or foot drop.

Unfortunately relatively few reports have been made regarding the cerebrospinal fluid. If an examination is mentioned, slight abnormalities or none at all have been recorded. There may be moderate pleocytosis (5 to 20 lymphocytes per cubic millimeter) and a slight increase in the total protein content, with curves for mastig precipitation which are either flat or nearly so.

The blood picture, if altered at all, includes a slight reduction in the hemoglobin content and in the number of erythrocytes, with moderate leukocytosis. In some cases eosinophilia occurs, with a usual maximum of 5 per cent, although extremes of 10 or 15 per cent have been noted.

The urine is generally normal.

The reaction to the tuberculin test was recorded in twenty-one of the sixty-six cases reviewed by Savin, with seven positive results. In the sixty-six cases the Wassermann reaction of the blood was mentioned in thirty-one instances—twenty-nine negative, two positive and two doubtful results.

REPORT OF CASES

Although Hamburger and Schaffer³ reported a case of uveoparotid fever from the Johns Hopkins Hospital in 1928, attention was not drawn

to the possibility of other cases until 1933, when the diagnosis was proposed by a visiting physician from South Africa in the following case

CASE 1—P P, a Negress aged 20, was seen in the medical clinic in the division for syphilitic patients on Feb 18, 1933, when convalescent from an illness for which a diagnosis of polyneuritis had been made. There was no suggestion of tuberculosis in her past and family histories. In childhood she had mumps. Manifestations of secondary syphilis appeared early in 1932. In April, after eight injections of neoarsphenamine were given, uveitis developed. This was followed in May by headache, weakness, vague abdominal pains, swelling of one side of the face and pain on moving the jaw. Paresthesias of the extremities, with signs of diffuse polyneuritis, soon appeared, and hospitalization was necessary. The Wassermann reaction of the blood was negative. The cerebrospinal fluid and urine were entirely normal. There was an essentially normal blood picture, excepting for 4 per cent eosinophils.

No facial paralysis appeared, although the facial swelling and tenderness suggested parotitis. There was a slight irregular fever, with the temperature ranging up to 99.8 F. Although the original impression was arsenical polyneuritis following antisyphilitic treatment, the possibility of atypical uveoparotitis was considered.

Although a positive diagnosis of uveoparotitis could not be made, the case provided the stimulus for future observations.

CASE 2—M W, a Negress aged 21, was admitted to a medical ward of the Johns Hopkins Hospital on Nov 25, 1933, complaining of headache, nausea, vomiting and vague abdominal pains of six weeks' duration. Her stepfather died of pulmonary tuberculosis, and a brother was a patient in a local hospital with active pulmonary tuberculosis. The patient had measles and pertussis in childhood. There was no history of mumps. She was married at the age of 18 and shortly afterward had a cutaneous eruption, with a positive Wassermann reaction. A practitioner gave her a single intravenous injection. Her husband was known to be under treatment for latent syphilis in this clinic.

In August 1933 her illness began with malaise, fatigability, slight edema of the ankles and occasional bilateral earache. One month later bilateral parotid swelling occurred and progressed until the glands were "even with the ears." The swellings disappeared within a week. The patient gave no history of contact with mumps. Within two weeks headache in the frontal region, anorexia, nausea, vomiting and abdominal pains began. A pain in the chest was diagnosed as due to pleurisy. Two weeks later weakness of the left side of the face was observed, followed by marked thirst, an increased intake of fluid and an increased output of urine. By November difficulty in swallowing, hoarseness and regurgitation of fluids through the nose had become marked. The patient began to experience "pins and needles" sensations over the entire right side of the body. Two days before her admission to the hospital weakness to the point of prostration and stiffness of the neck were noted.

Physical Examination—The temperature was 101.6 F, the pulse rate 130 and the respiratory rate 30 per minute. There was extreme weakness, with signs of dehydration and loss of weight. The neck was stiff. The pupils were dilated and equal and reacted sluggishly. No extra-ocular paralysis was found. The retinal veins were engorged. All the parotid swelling had disappeared, but most of the cervical lymph nodes were enlarged. The gums were bleeding. Examination revealed harsh breath sounds and persistent râles in the upper lobe of the right lung. Cardiovascular examination showed only tachycardia and a blood pressure

of 150 systolic and 100 diastolic. Diffuse abdominal tenderness was noted. In addition to stiffness of the neck, the neurologic examination revealed complete paralysis of the left side of the face of peripheral type, paralysis of the left side of the uvula, unequal knee jerks, bilateral ankle clonus, a questionable Kernig sign and no Babinski sign. Encephalitis and acute syphilitic meningitis were strongly suspected.

Laboratory Examination—The urine showed a specific gravity of 1.010, some albumin, no sugar, many hyaline casts and a few leukocytes and erythrocytes. These abnormalities disappeared gradually within three weeks.

Examination of the blood showed hemoglobin, 10.8 Gm per hundred cubic centimeters, erythrocytes, 3,400,000, and leukocytes, 10,000. The differential count was essentially normal. The leukocyte count varied from 10,000 to 14,000 for



A patient (case 2) with uveitis, weakness of the right side of the face and swelling of the parotid and lacrimal glands.

several weeks, with 3 per cent eosinophils. The Wassermann and flocculation tests gave positive results.

The cerebrospinal fluid was clear and colorless and under normal pressure. It was free from micro-organisms, as shown by smear and culture. There were 15 lymphocytes. The Wassermann reaction was negative with 0.2 cc and doubtfully positive with from 0.4 to 1 cc of fluid. The total protein content was 38 mg per hundred cubic centimeters, the curve for the mastix precipitation was 0.133100000 and the sugar content was 78 mg per hundred cubic centimeters. Two weeks after the patient's admission to the hospital the cerebrospinal fluid gave a completely negative Wassermann reaction but showed 9 lymphocytes, a total protein content of 50 mg per hundred cubic centimeters and a curve for mastix precipitation of 5554320000.

Chemical analysis showed essentially normal blood except that the non-protein nitrogen content was 39 mg per hundred cubic centimeters shortly after the patient's admission to the hospital

Roentgenologic studies showed that the sella turcica was normal. A small area of infiltration was seen in the upper lobe of the right lung when the patient was admitted and two weeks later areas of consolidation were noted in both hilar regions. These were interpreted as being due to tuberculous involvement. The reaction to the tuberculin test was negative with 0.01 and 0.1 mg of old tuberculin intracutaneously administered.

Course—After admission to the hospital the patient showed increasing stupor, and on the second day three generalized convulsions occurred. Delirium, hallucinations and a temperature up to 103 F characterized this period. By the second week the blood pressure had fallen to a normal level, and the mental status was calm. Signs of involvement of the lower lobe of the right lung appeared. In the third week complete palsy of the right side of the face of peripheral type was present, while there was residual weakness of the left side. The reflexes were normal, but stiffness of the neck, with occasional nausea and vomiting, persisted.

In December, one month after the patient's entry, there was an increase in the intra-ocular tension (right eye, 55 mm of mercury, left eye, 47 mm—Schiotz). The media of the right eye were hazy, and the cornea became dull, the sclera injected and the eye painful. The visibility of the aqueous ray was increased in both eyes. Paracentesis of the anterior chambers was performed, followed by iridotaxis. Slit lamp examination showed numerous fatty deposits on the anterior surface of the lens and on the posterior surface of the cornea of the left eye. Inoculations of guinea-pigs with the aqueous fluid gave negative results. The ophthalmologic diagnosis was bilateral uveitis and secondary glaucoma.

In January 1934 the sputum showed tubercle bacilli on five occasions. A long period followed with continued low grade fever, the temperature not exceeding 99.8 F. Physical and roentgenologic examinations showed extensive infiltration of the entire right lung, with thickening of the pleura. Five months after the patient's admission to the hospital there was a period of slight general improvement, and then the afternoon fever recurred, the temperature reaching a maximum of 101 F. The condition of the eyes improved, and examination in May 1934 showed a normal tension and no corneal deposits, with only postoperative pupillary defects and haziness of the media of the right eye. There was residual facial weakness on the right, and signs of infiltration of the right lung persisted.

Before tubercle bacilli were noted in the sputum, treatment was entirely symptomatic, except for the administration of iodides in considerable quantities and for half a dozen injections of a bismuth compound at odd times during the five months of hospitalization.

The patient was transferred to a sanatorium for tuberculous patients in June 1934, and her condition remained unchanged until October. She left of her own accord in November and reappeared at the Johns Hopkins Hospital, where she was reexamined at the clinic on December 13. She was obviously ill, and admission to a medical ward was requested, with the diagnosis of uveoparotitis.

It was found that a swelling of the parotid glands had recurred in October that was identical with that of the previous year. The right parotid gland became swollen first, followed a week later by swelling of the left gland. Both were hard and tender to pressure and were not adherent to the skin or underlying tissues. A daily elevation of temperature occurred. Although bilateral facial weakness

was observed at first, it became more marked on the left. The speech became mushy, and chewing was difficult. In November difficulty in closing the eyelids was noticed.

Physical Examination—At the time of the patient's second admission to the hospital there was a temperature of 100 F, with slight acceleration of the pulse and respiratory rates. There was a scaly desquamation over the tibiae. The parotid, lacrimal, sublingual and submaxillary glands, as well as the posterior cervical and axillary lymph nodes, were enlarged. Examination of the eyes showed injection of the conjunctivae and sclera, cloudiness of the anterior chamber and numerous mutton-fat deposits over the anterior capsule of the lens and the posterior surface of the cornea. The pupils were unequal, deformed and fixed. The fundi could not be seen clearly. The intra-ocular tension was normal. There was bilateral facial weakness, and the uvula was deviated to the left. Signs of infiltration of the right lung were present. No other general or neurologic abnormalities were detected.

Laboratory Examination—The urine exhibited a trace of albumin and a few hyaline casts but became normal within two days.

The blood showed a normal erythrocyte count and hemoglobin content. The leukocytes numbered 9,000, with 69 per cent polymorphonuclear cells, 9 per cent being eosinophils. (Six weeks after the patient's admission to the hospital a maximum of 13 per cent eosinophils was noted, but for only a few days.) The Wassermann reaction of the blood was doubtful, but the flocculation test was positive.

The cerebrospinal fluid was clear, colorless and under normal pressure and contained 6 lymphocytes. The total protein content was 25 mg per hundred cubic centimeters, and the curve for mastic precipitation was 333210000.

The sputum persistently showed tubercle bacilli. The reaction to the test with tuberculin, 0.1 mg administered intracutaneously, was negative. Culture of catheterized secretion from the parotid gland yielded no growth. Electrocardiographic examination revealed no abnormality.

Course—Small doses of neoarsphenamine were administered, but a generalized maculopapular rash with itching followed the third injection. This disappeared with cessation of treatment. Three weeks after the patient's admission to the hospital roentgen therapy was attempted for the parotid and lacrimal swelling. After the second treatment intense swelling and edema of the glands occurred, and roentgen therapy was abandoned. The sublingual tissues remained markedly edematous and resembled a false tongue for many weeks. Low grade fever persisted, the temperature averaging 99.6 F. After three months the lacrimal and parotid swellings had practically disappeared.

In June 1935 the essential findings were facial weakness on the right, enlargement of the sublingual glands, slight enlargement of the lacrimal gland, and signs of infiltration at the base of the right lung.

The patient was sent to the Tuberculosis Hospital of the Baltimore City Hospitals in September. Fever and tachycardia continued. Although signs suggestive of pleural effusion were noted at the base of the right lung, repeated thoracentesis revealed no fluid. The sputum persistently showed no tubercle bacilli. A course of neoarsphenamine was administered during a period of apparent general improvement. In January 1936 the patient's condition was increasingly unfavorable, and death occurred approximately two years and four months after the onset of the illness. Extreme weakness, hoarseness, edema of the ankles and bleeding by mouth marked the terminal illness. All efforts to obtain permission for autopsy were unsuccessful.

CASE 3—M P, a Negress aged 24, was seen in the Wilmer Ophthalmological Institute on July 31, 1934, complaining of headache and painful inflammation of the eyes of three weeks' duration. During that time there had been swelling of the eyelids each morning, and for one week she had experienced regurgitation of fluids through the nose, numbness of the face and an inability to smile. The speech had become mushy. For nearly a year there had been "nervous indigestion," with a loss of 20 pounds (9 Kg). Her past history showed only pertussis and measles in childhood, and no suggestion of mumps, tuberculosis or syphilis could be elicited.

Physical Examination—On August 9 the patient became obviously ill and was admitted to a medical ward of the Johns Hopkins Hospital. The temperature was 99.6 F, the pulse rate 96 and the respiratory rate 20. Although very restless, the patient was alert and cooperative. No cutaneous lesions were visible. Although no parotid enlargement was detected, the patient insisted that the right side of her face was fuller than usual. The lymph nodes at the angles of the jaw were palpable. Examination of the eyes showed a normal intra-ocular tension, pericorneal injection and irregularity of the left pupil, with posterior synechiae. The slit lamp revealed a strongly positive aqueous ray, with numerous amorphous deposits in the endothelial layer of the cornea, a muddy, edematous iris, with deposits of pigment over the anterior capsule of the lens of the left eye. Vision in the right eye was 20/70 and in the left eye 20/200 uncorrected. The ophthalmologist made a tentative diagnosis of acute uveitis, possibly due to syphilis. There was slight tenderness on pressure near the right ear in the parotid region.

Examination of the heart, lungs and abdomen showed no abnormalities. Neurologic examination revealed impairment of sensation on both sides of the face and neck, absence of the corneal reflexes, bilateral facial weakness, more marked on the right, poor movement of the uvula, and absence of the knee and ankle jerks. The diagnoses suggested were meningitis or bulbar palsy, with uveitis, due to syphilis.

Laboratory Examination—The blood picture was not remarkable. The leukocytes numbered 9,000, with 1 per cent eosinophils. The Wassermann test of the blood was negative, but the flocculation test was positive. The cerebrospinal fluid was clear and colorless and under normal pressure. There were 10 lymphocytes, and the total protein content was 37 mg per hundred cubic centimeters. The curve for mastic precipitation was 0011110000. The Wassermann reaction was negative. Five days later an examination of the cerebrospinal fluid gave the same results, except for a lymphocyte count of only 3 cells per cubic millimeter. The urine was normal. The reaction to the tuberculin test was negative (old tuberculin, 0.001 and 0.01 mg intracutaneously). Roentgenologic studies showed signs of old mediastinal tuberculosis.

Because of uveitis associated with tenderness and questionable swelling in the region of the parotid glands, involvement of the cranial nerves, reduction of the deep tendon reflexes and fever, uveoparotitis was considered as a possible diagnosis.

Course—Shortly after the patient's admission to the hospital the temperature reached a maximum of 102 F but soon fell to a maintained average of 99.5 F. Four small injections of neoarsphenamine were administered together with potassium iodide by mouth, salicylates and atropine were employed for the uveitis. By the time of the patient's discharge, on August 27, there had been a general improvement, although traces of uveitis, absence of the corneal reflexes and facial weakness persisted.

The patient was followed in the syphilis division of the medical clinic and in the outpatient department of the Wilmer Ophthalmological Institute. Anti-

syphilitic treatment was continued with arsenicals and bismuth for more than a year. While the ophthalmologists felt that syphilis was probably responsible for the uveitis, the staff of the syphilis division held the opposite opinion. By the end of 1934 only facial weakness and chronic uveitis were present. Throughout 1935 low grade uveitis persisted, and paracentesis of the aqueous of the right eye became necessary on two occasions. Deep marginal invasion of the cornea was suggestive of a tuberculous etiology, although there was relative insensitivity to tuberculin. Periods of improvement were apparently associated with arsenical therapy, but the possibility of the nonspecific reaction of arsenicals in uveitis (Stokes and O'Leary) was kept in mind. In spite of fairly regular antisyphilitic treatment, frequent exacerbations of the uveitis occurred during the last period of observation in 1936.

CASE 4—B. S., a Negress aged 31, was seen in the Wilmer Ophthalmological Institute on March 27, 1935, complaining of painful sore eyes and facial weakness, with headache in the frontal region of one month's duration. There had also been anorexia, nausea and vomiting. The right side of the face became paralyzed on March 26, and fainting occurred once on that date. She gave a history of mumps, whooping cough, measles and chickenpox in childhood, but nothing suggestive of tuberculosis or syphilis could be elicited.

Physical Examination—The patient was admitted immediately to a medical ward of the Johns Hopkins Hospital. Examination showed that the temperature, pulse and respirations were normal. No cutaneous eruption was seen. The axillary and inguinal lymph nodes were palpable. The parotid glands were not enlarged. Examination of the eyes showed a normal intra-ocular tension. With the slit lamp numerous deposits typical of punctate keratitis were observed on Descemet's membrane and in the anterior capsule of the lens of both eyes. The pupils were irregular and did not react well to light. Posterior synechia also was noted. Numerous opacities of the vitreous were seen. The fundi were normal. The only other abnormalities were found on neurologic examination. These consisted of complete peripheral facial palsy on the right, with a loss of the sense of taste on the anterior two thirds of the tongue, and sluggishness of the abdominal reflexes. The diagnostic impression was uveitis, with meningitis (?), probably syphilitic in origin.

Laboratory Examination—The blood was normal, but the Wassermann reaction was positive. The cerebrospinal fluid and urine were entirely normal. No tuberculin test or roentgenograms were made.

Course—Routine antisyphilitic treatment was begun. The patient was discharged, improved, with residua of the iritis on April 13. She was followed in the syphilis division, and the Wassermann reaction became negative within a few weeks. Treatment was pursued until January 1936, after which the patient was never seen.

CASE 5—E. A., a Negress aged 28, was admitted to a medical ward of the Johns Hopkins Hospital on July 8, 1935. She complained of swelling of the face, difficulty in swallowing and regurgitation of liquids through the nose. The past history was unimportant, except for an illness diagnosed as pleurisy when she was 16 years old. There was no history of mumps. The illness had been present for seven weeks, with anorexia, eructation after meals, vertigo and malaise. This was followed by simultaneous swelling of both sides of the face, with aching and soreness of the throat. Vomiting occurred frequently. One week before the patient's admission to the hospital there developed hoarseness, a nasal voice,

dysphagia and regurgitation of fluids through the nose when an attempt was made to swallow. During the illness 12 pounds (5.5 Kg.) of weight was lost.

Physical Examination—Examination showed that the temperature was 101 F., the pulse rate 110 and the respiratory rate 24 per minute. Weakness was extreme, and there was evidence of dehydration. No cutaneous eruption or enlargement of the lymph nodes was found. The parotid glands were enlarged symmetrically and were firm but not tender. There was no attachment to the skin or underlying tissues. Examination of the eyes showed abnormalities only in the right eye, in which vision was limited to counting fingers at 1 foot (30 cm.). Abnormalities were noted only on ophthalmoscopic examination. The margins of the disks were blurred, with indistinct cupping and marked neuroretinal edema. Several small, round spots of grayish exudate were seen in the region of the macula, and there were areas of old chorioretinal atrophy. The veins were full and tortuous, the arteries were narrowed and arteriovenous compression was marked. While the exudate was considered to be suggestive of tuberculosis, certain perivascular changes were thought to be characteristic of syphilis.

The remainder of the physical examination gave essentially normal results, except for the neurologic findings. These consisted of complete peripheral facial palsy, with weakness of the uvula and uveal cord, on the right, and of hypo-active deep tendon reflexes.

Laboratory Examination—The blood picture was essentially normal. The Wassermann reaction was doubtful on repeated tests. The cerebrospinal fluid was clear and colorless and was under normal pressure. It showed 8 lymphocytes and a normal total protein content. The Wassermann reaction was positive with 0.4 cc., and the curve for mastic precipitation was entirely negative. The sputum repeatedly showed no acid-fast bacilli. The reaction to the tuberculin test was positive with 1 mg. of old tuberculin administered intracutaneously, but it was negative with smaller amounts. Roentgenologic studies showed markedly accentuated shadows of the roots of the lungs, with thickening of the pleura, which were interpreted as having a tuberculous origin. The skull and sella were normal. Gastro-intestinal studies showed no abnormalities.

Course—The temperature ranged from 101 to 102 F. for two weeks. It was discovered that the odors of tobacco and ammonia could not be detected. The parotid swelling, facial weakness and hoarseness disappeared by the third week, and a few days later no abnormalities existed other than the anosmia and the changes in the right fundus. Five weeks after the patient's admission to the hospital examination revealed definite deposits on Descemet's membrane, with an increase in the visibility of the aqueous ray, in both eyes. The right disk was blurred and edematous. Vision in the right eye was 10/120, and that in the left eye was 20/30 at that time. Treatment, other than symptomatic, consisted of weekly injections of neoarsphenamine.

The patient was discharged to the care of the syphilis division on August 31, and antisyphilitic treatment of the routine type was continued. Serologic tests were negative in October, and the ocular condition was quiescent. In December an indurated erythematous eruption appeared on the legs, and this was diagnosed as erythema nodosum. Roentgenologic studies showed an increase in the shadows of the roots of the lungs. The ocular status was quiescent, and at the last observation early in the spring of 1936 no remarkable changes were noted in the general condition of the patient.

CASE 6—M. F. J., a Negress aged 32, a native of North Carolina, came to the medical clinic of the Johns Hopkins Hospital on Aug. 23, 1935, complaining of

malaise and weakness of more than a year's duration. The past and family histories revealed nothing of importance before the onset of her complaints.

Beginning in February 1934 the patient had vague abdominal pain, malaise and weakness, with amenorrhea for three months. In November the right parotid and submaxillary glands were swollen, and this was followed quickly by severe headache, stiffness of the neck, weakness of the right side of the face and inability to swallow solids. These difficulties disappeared within two weeks, except for residual facial weakness and marked lassitude, accompanied with an afternoon temperature of 99 or 100 F during the autumn. She was studied at the Duke University Hospital, Durham, N. C., in February 1935, where the findings consisted of "arrested pulmonary tuberculosis, secondary anemia, residual Bell's palsy on the right and iridocyclitis." Roentgenologic studies of the chest in that clinic revealed several enlarged rounded areas which were regarded as enlarged hilar nodes. A supraclavicular node was removed, and the biopsy report by Dr. Roger Baker, associate professor of pathology described "an epithelioid cell reaction, probably tuberculous." No tubercle bacilli were observed in the sections.

Physical Examination—The patient was examined at the University of Pennsylvania Hospital in April 1935. At that time there were undernutrition, low grade fever, enlarged cervical and supraclavicular nodes, anisocoria with posterior synechia, residual peripheral facial palsy on the right and enlarged hilar nodes, which were thought to be tuberculous. The uveitis was considered to be of tuberculous origin. The blood, cerebrospinal fluid, sputum and urine were entirely normal. Sections of the lymph node (previously made at the Duke University Hospital) were interpreted as showing "chronic adenitis very suggestive of tuberculosis."

The patient experienced numbness in the right arm and pain in the left side of the chest and had an unproductive cough, with anorexia, in the summer of 1935. Examination at the medical clinic of the Johns Hopkins Hospital on August 23 showed the temperature to be 99.4 F, with slight tachycardia. The glands at the angles of the jaw were enlarged slightly. There was old bilateral uveitis. With the slit lamp numerous mutton-fat deposits could be seen on the posterior surface of the corneas. There was increased retromanubrial dullness, and it was impossible to obtain a blood pressure reading in the right arm. Residual facial paralysis on the right constituted the remaining abnormality.

Laboratory Examination—Serologic tests for syphilis were negative. The blood and urine were normal. The reaction to the tuberculin test was positive with 1 mg. of old tuberculin injected intracutaneously. Roentgenologic studies confirmed those previously described.

Course—Roentgen treatment was undertaken for the mediastinal mass, with no visible change. Tuberculin therapy was begun, and the patient was returned to her home to continue the course of treatment. In May 1936 her physician stated that no appreciable change had occurred in the general condition or in the roentgenologic picture of the chest following a long course of tuberculin therapy.

COMMENT

The cases of six young Negroes are presented who showed a syndrome suggestive of or identical with that described as uveoparotitis, or uveoparotid fever. In four there was evidence of tuberculous infection. In five syphilis was evidenced by the history, physical findings or posi-

tive results of serologic tests. The diagnosis of acute syphilitic meningitis was proposed for three during the acute stage of the illness.

In no instance did examination of the cerebrospinal fluid support the initial impression of acute syphilitic meningitis, and in only one instance was there evidence of invasion of the central nervous system by syphilis. Such abnormalities as were discovered consisted of slight pleocytosis and a mild increase in the total protein content.

Parotitis was an outstanding finding in three of the patients and in case 2 a recurrence was an unusual feature. In two cases definite parotitis was questionable, and in one it was not observed. The type of parotitis seen in these cases corresponded closely with that described in the literature as occurring in uveoparotitis. With regard to the possibility of syphilitic etiology, Kemp and Moore¹⁵ found involvement of the salivary glands in less than 0.07 per cent of the syphilitic patients at the Johns Hopkins Hospital.

Syphilitic parotitis¹⁶ may be of three types. In early syphilis the gland swells rapidly and is tender to the touch and firm, with a tense, tender, reddish surface. The swelling is usually bilateral but not symmetrical. Suppuration occasionally occurs in the neighboring lymph nodes. The mass is closely adherent to the underlying tissues. Salivation, pain and dysphagia are prominent. Fever is rare. The infection may last for from two to twelve months.

In late syphilis parotitis develops insidiously. The tumor mass becomes attached to the underlying tissues and the skin. Fluctuation develops, with the appearance eventually of a gummatous ulcer. In congenital syphilis the lesion in the parotid gland is commonly a diffuse fibrosis. The gummatous type of lesion responds well to antisyphilitic treatment.

In two of the cases reported here it was possible to observe the character and course of the parotitis, which in these instances was unlike a syphilitic process. In two other cases parotitis was mild and transient, if existent, and in another case it was mild and of short duration.

The etiology of the ocular lesions is a most interesting question. In cases 2 and 6 the ophthalmologists were of the opinion that tuberculosis was the causative factor. Case 3 was the subject of considerable controversy, with arguments both for and against syphilis and tuberculosis. In case 5 the lesion was neuroretinitis, which has been described as occurring infrequently in uveoparotitis. There was lack of evidence of tuberculosis and improvement of the iritis with antisyphilitic treat-

15 Kemp J. E., and Moore, J. E. Syphilis of the Salivary Glands, *Arch Dermat & Syph* 6: 57 (July) 1922.

16 Chargin, L., and Rosenthal, T. Syphilitic Parotitis, *Arch Dermat & Syph* 24: 236 (Aug.) 1931.

ment in case 4. No adequate data relating to the possible tuberculous etiology of the ocular manifestations were available in case 1.

Fever was present in five of the six cases presented here and was of many months' duration in two of these cases.

Facial paralysis occurred in five of the cases. Additional neurologic abnormalities have been described in the individual case reports. The first case of the series, in which the condition was characterized by uveitis and diffuse polyneuritis, must be regarded as unusual or as representing a *forme fruste*, if it is included as a case of uveoparotitis. The possibility of arsenical polyneuritis cannot be overlooked.

A review of the literature reveals a multiplicity of causes to which uveoparotitis has been ascribed, including tuberculosis, syphilis, beriberi, mumps, diphtheria, oral sepsis and "pseudoleukemia." It has been designated also as a variety of the Mikulicz syndrome. Most of these theories have been discarded, leaving two schools of thought. The question now stands as to whether the established clinical entity is due to tuberculosis or to some undiscovered infectious agent such as a virus. Garland and Thomson have advanced considerable evidence in favor of tuberculosis. This includes postmortem observation of miliary tubercles (four cases), biopsy of the iris (four cases), bulbar conjunctiva (one case), focal reaction to tuberculin (two cases) and pulmonary tuberculosis with positive findings in the sputum (one case). These authors declared in 1933 that they had found incontrovertible evidence of tuberculosis in more than one third of the recorded cases.

It is true that it has been impossible to demonstrate tubercle bacilli in biopsy sections of the parotid, lymphoid and ocular tissues, although such sections commonly show histologic evidence of a fibrosing endotheioid lesion that is highly suggestive of tuberculosis. Cavard injected such material intraperitoneally into guinea-pigs, producing fatal generalized tuberculosis in one instance. Collateral evidence of tuberculosis is more common in the form of the family history, pleural effusion, roentgenologic evidence, cervical adenitis and the reaction to tuberculin injected intracutaneously.

It is singular that five of the six patients reported on in this paper showed evidence of syphilis by serologic reaction, in the light of the fact that this infection has been recorded rarely in the cases of uveoparotitis previously reported. As far as can be determined, all previously reported cases have been in the white race, whereas this group is composed entirely of young Negroes. Thirty or 40 per cent of an unselected number of Negro hospital patients in this locality will show positive results of serologic tests for syphilis. The incidence of tuberculosis in Negroes of this city also is high. Syphilis is no longer

considered seriously as an etiologic agent in uveoparotitis, and in the present group of cases the infection is considered as being entirely coincidental

As stated previously, the first case of uveoparotitis in this hospital was reported by Hamburger and Schaffer in 1928. At that time the authors gave as their opinion that the condition represented a form of the Mikulicz syndrome. They were unable to discover evidence of tuberculosis at that time. They have recently granted me permission to state that in their patient renal tuberculosis subsequently developed, for which nephrectomy was performed.

In conclusion, it appears that the more fully cases are investigated, the more evidence one finds in favor of tuberculosis.¹⁷ Garland and Thomson seemed to be justified in designating the syndrome as uveoparotid tuberculosis, and the burden of proof is on those who favor an unknown virus as the causative agent.

SUMMARY

Six cases of patients presenting the syndrome of uveoparotitis or uveoparotid fever, all young Negroes, are reported.

Five of these patients had syphilis and four tuberculosis. Three had both of these infections.

The weight of evidence favors the tuberculous etiology of uveoparotitis.

NOTE—M. P. (case 3) was seen on Nov. 18, 1936, and she complained that she had suffered from a severe cough for seven weeks. There had been no loss of weight, and the temperature had been normal. Physical and roentgenologic examination showed evidence of infiltration of the upper lobe of the right lung suggestive of pulmonary tuberculosis. Examination of the sputum revealed no tubercle bacilli.

17 Uveo-Parotid Tuberculosis, editorial, *Lancet* 2:763, 1934.

RELATION OF EXPERIMENTAL ATHEROSCLEROSIS TO DIETS RICH IN VEGETABLE PROTEIN

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In 1920 Newburgh and Squier¹ reported the occurrence of atherosclerosis in rabbits fed diets rich in animal protein. The diets used were of two kinds: one was a mixture of milk, scraped carrot and water to which casein was added, the other was a mixture of dried powdered beef and bread flour in the proportion 1:2. Although it appeared that the vascular lesions had been caused by the protein of the diets, such a conclusion was thought not to be warranted at that time because of the smallness of the group of experimental animals.

Later, investigation by Newburgh and Clarkson² showed conclusively that ingestion of muscle meat by rabbits results in extensive atherosclerosis of the aorta and other large arteries. Eight of eleven animals that were fed a diet containing 27 per cent protein derived chiefly from dried ground beef muscle for more than six months became atherosclerotic. In all the rabbits that were fed a diet containing 36 per cent protein derived chiefly from beef muscle for from eighteen to thirty-six weeks marked and extensive atherosclerosis developed. The occurrence and extent of the sclerosis were roughly proportional to the duration of the feeding of meat.

Since it had been shown by others³ that feeding of cholesterol causes atherosclerosis in rabbits, it was suggested by some that the cholesterol contained in the meat diets caused the vascular lesions. Clarkson and Newburgh⁴ showed, however, by the addition of different amounts of

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1 Newburgh, L. H., and Squier, T. L. High Protein Diets and Arteriosclerosis in Rabbits. A Preliminary Report, *Arch Int Med* **26** 38 (July) 1920

2 Newburgh, L. H., and Clarkson, S. The Production of Atherosclerosis in Rabbits by Feeding Diets Rich in Meat, *Arch Int Med* **31** 653 (May) 1923

3 Anitschkow, N., and Chalutow, S. Ueber experimentelle Cholesterinsteatose, *Centralbl f allg Path u path Anat* **24** 1, 1913. Wacker, L., and Hueck, W. Ueber experimentelle Atherosklerose, *Munchen med Wchnschr* **60** 2097, 1913. Kon, J. Experimentelle Atherosklerose, *Tr Jap Path Soc* **3** 8, 1913. Bailey, C. H. Atheroma and Other Lesions Produced in Rabbits by Cholesterol Feeding, *J Exper Med* **23** 69, 1916

4 Clarkson, S., and Newburgh, L. H. The Relation Between Atherosclerosis and Ingested Cholesterol in the Rabbit, *J Exper Med* **43** 595, 1926

cholesterol to normal diets, that the amount of cholesterol contained in the diets high in beef protein was too small to produce by itself hypercholesteremia or atherosclerosis. It was necessary to add ten times the amount of cholesterol found in the meat diets before atherosclerosis resulted. In this same investigation it was pointed out that animals in which atherosclerosis developed as a result of ingestion of beef muscle had, in every case, hypercholesteremia. This finding suggested, therefore, that the hypercholesteremia resulted from cholesterol synthesis within the body, caused in some way by the ingestion of diets high in meat, and that the vascular lesions resulted from the hypercholesteremia.

In order to investigate this problem further the following experiments were performed. It was desired to learn whether atherosclerosis would result from feeding diets rich in vegetable protein as it did from feeding muscle meat and, if it would, whether hypercholesteremia preceded the appearance of the vascular lesions.

EXPERIMENTAL METHOD

Three diets containing different amounts of vegetable protein were prepared as follows:

Diet 1	Gm
Ground whole soy bean	600
Corn starch	1,000
Alfalfa meal	400
Sodium chloride	12
Diet 2	Gm
Ground whole soy bean	1,200
Gluten flour	400
Alfalfa meal	400
Sodium chloride	12
Diet 3	Gm
Gluten flour	1,600
Alfalfa meal	400
Sodium chloride	12

To each of these diets baking powder and water were added, and the mixture was kneaded into a dough and baked in an oven at 180 F until a brown crust formed.

Samples of each diet (after baking) were analyzed for nitrogen by the Kjeldahl method. Diet 1 contained 2.3 per cent nitrogen, diet 2 5.8 per cent and diet 3 6.64 per cent. Using Jones'⁵ factors for converting percentages of nitrogen

⁵ Jones, D. B. Factors for Converting Percentages of Nitrogen in Foods and Feeds into Percentages of Proteins, U. S. Dept. Agric., circular 183, 1931, p. 6.

in soy beans and wheat flour into percentages of proteins,⁶ the protein of each diet was calculated to be

	Protein, %
Diet 1	13.1
Diet 2	33.0
Diet 3	37.8

It should be noted that these diets contained no animal food, consequently they contained no cholesterol. Schonheimer⁷ has shown that plant sterols (phytosterol) are absorbed in infinitesimal amounts, if at all. These diets are therefore "metabolically" sterol free, so that any abnormality that might result from feeding such diets could not be ascribed to dietary sterol.

Eighteen rabbits approximately 4 months old were selected for this study. These animals were kept in individual cages. They were divided into three equal groups, each group receiving a different diet. Twice weekly the diet was supplemented by a feeding of lettuce or carrots. In order to avoid a deficiency of vitamin D, the rabbits were given ultraviolet radiation, each animal receiving the equivalent of approximately 1 human skin erythema dose weekly.

At intervals the animals were weighed and bled from the marginal vein of the ear. Five cubic centimeters of blood was removed on each occasion, clotting being prevented by the use of sodium oxalate. The whole oxalated blood was analyzed for its cholesterol content by the oxidative digitonin method of Okey.⁸ After various lengths of time the animals of each group were killed, and the large arteries were examined grossly and microscopically for evidence of atherosclerosis.

RESULTS

All the animals fed diets 1 and 2, which were crumbly and had a pleasing taste, ate heartily from the outset and rapidly increased in weight, in fact, some became obese. The rabbits fed diet 3, which was hard and tasteless, ate sparingly during the early part of the study, during which time they either lost weight or grew only a little. After about three months they began to eat well and gained in weight. It will be shown later that these differences in the nutritional state of the animals are important.

The cholesterol values and autopsy observations are summarized in the accompanying tables.

6 In soy beans the amount of nitrogen multiplied by 5.71 equals the amount of protein. In wheat the amount of nitrogen multiplied by 5.7 equals the amount of protein.

7 Schonheimer, R. Ueber die Bedeutung der Pflanzensterine für den tierischen Organismus. Ueber die Sterine des Kaninchenkotes, *Ztschr. f. physiol. Chem.* **180** 32, 1929. Schonheimer, R., von Behring, H., Hummel, R., and Schindler, L. Ueber die Bedeutung gesättigter Sterine im Organismus, *ibid.* **192** 73, 1930.

8 Okey, R. A Micromethod for the Estimation of Cholesterol by Oxidation of the Digitonide, *J. Biol. Chem.* **88** 367, 1930.

TABLE 1—*Weight, Cholesterol Values of the Blood and Condition of the Aorta of Animals Fed Diet 1, Containing 13.1 Per Cent Vegetable Protein, Chiefly from Soy Beans*

Animal	Sex	Day of Experiment	Weight, Kg	Blood Cholesterol, Mg per 100 Cc	Condition of Animal When Killed	Condition of Aorta
1	M	1 48	1.80	86	"Snuffles"	Normal
2	M	5 82 124	1.50 2.26 2.60	67 76 80	Healthy	Normal
3	M	38 138 192	2.68 3.70 3.70	74 64 119	Healthy	Normal
4	M	43 120 228	2.25 3.52 4.20	57 73 50	Healthy	Normal
5	M	1 43 120 228 281	1.88 1.97 2.35 2.85 2.93	72 69 85 85 67	Healthy	Normal
6	M	1 43 120 228 281	1.94 2.11 2.66 3.20 4.48	87 69 124 82 71	Healthy	Normal

TABLE 2—*Weight, Cholesterol Values of the Blood and Condition of the Aorta of Animals Fed Diet 2, Containing 33 Per Cent Vegetable Protein, Chiefly from Soy Beans and Gluten Flour*

Animal	Sex	Day of Experiment	Weight, Kg	Blood Cholesterol, Mg per 100 Cc	Condition of Animal When Killed	Condition of Aorta
11	M	1 38 99 159	2.00 2.40 2.80 3.15	87 89 91 84	Healthy	Normal
12	M	1 60 104 180 217	1.65 1.99 2.49 2.25 2.35	80 69 70 68	Bubo on neck	Normal
13	M	1 44 120 228	2.40 2.61 2.62 3.15	110 77 70 70	Healthy	Normal
14	M	1 31 92 168 276	1.60 2.00 2.75 3.07 4.10	98 85 67 54	Healthy	Normal
15	M	23 92 168 286 346	1.90 2.52 3.05 3.05	69 90 79	Healthy	Normal
16	M	1 60 104 180 288 349	2.27 2.42 2.90 2.90 3.50 3.15	86 85 80 67 134	"Snuffles"	Normal

None of the animals showed gross or microscopic evidence of atherosclerosis of the aorta or other large vessels. The level of cholesterol in the blood remained close to the preexperimental value in the majority of animals. Considering the range of 35 to 125 mg per hundred cubic centimeters found by Clarkson and Newburgh⁴ as normal, only rabbits 16, 21, 22, 23, 25 and 26 showed hypercholesteremia at any time. In none of the animals was the level of cholesterol in the blood very high, the highest value observed was 182 mg per hundred cubic centimeters,

TABLE 3—*Weight, Cholesterol Values of the Blood and Condition of the Aorta of Animals Fed Diet 3, Containing 37.8 Per Cent Vegetable Protein, Chiefly from Gluten Flour*

Animal	Sex	Day of Experiment	Weight, Kg	Blood Cholesterol, Mg per 100 Cc	Condition of Animal When Killed	Condition of Aorta
21	F	23	1.16	89	Undernourished	Normal
		147	2.20	170		
22	M	1	2.50	65	Healthy	Normal
		25	2.10			
		35		97		
		96	1.95	182		
		156	2.36	70		
23	F	23	1.05	73	Slightly undernourished	Normal
		147	1.88	126		
		209	2.20	154		
24	M	1	1.90	72	Healthy	Normal
		43		87		
		104	2.10	69		
		164	2.33	95		
		258	2.43	65		
25	M	1	2.05	95	Healthy	Normal
		36	1.50			
		43		106		
		104	1.70	156		
		164	2.50	137		
		258	3.12	104		
26	M	320	3.30	97	Healthy	Normal
		1	2.50	93		
		28	1.80			
		96	1.97	127		
		156	2.13	93		
		280	2.65	74		
		342	2.65	110		

found on the ninety-sixth day in rabbit 22. In three animals (rabbits 22, 25 and 26) the slight elevations of the cholesterol content of the blood occurred at the times the animals were considerably undernourished. They later began to eat heartily of the same high protein diet, they gained weight, and the cholesterol content of the blood returned to normal.

Only three animals had hypercholesteremia when killed. After two hundred and eighty-eight days with a normal cholesterol value, rabbit 16 contracted "snuffles" and its weight decreased from 3.5 to 3.15 Kg.

during the two months just prior to its death, when the slightly high value of 134 mg per hundred cubic centimeters was found. Rabbits 21 and 23 were younger and very small females when the feeding started. They increased in weight but were still undernourished when killed. The cholesterol values were 170 and 154 mg per hundred cubic centimeters, respectively, when the animals were killed.

COMMENT

Since hypercholesteremia was in every case associated with under-nutrition and since the cholesterol content of the blood returned to normal in every instance when a normal nutritional state again obtained, while the animals remained on the same high protein diets, the rare occurrence of hypercholesteremia evidently was not caused by the protein of the diets but resulted from malnutrition.

It is clearly shown that diets high in vegetable protein do not produce atherosclerosis. Diets 2 and 3 contained as much or more protein than did the beef muscle diets fed by Clarkson and Newburgh, which in every case caused atherosclerosis in from eighteen to thirty-six weeks. There are two possibilities which would explain the occurrence of atherosclerosis in rabbits fed on diets rich in animal protein and the absence of such vascular lesions in rabbits fed on diets high in vegetable protein. Either the animal protein itself when fed to rabbits causes this lesion, or there is a nonprotein constituent of these animal foods which is the etiologic agent.

The first of these explanations seems very unlikely. Complete analyses of the protein of beef muscle, gluten flour and soy beans are not available. Yet the analytic data that exist show the composition of these various proteins themselves to be such that the difference in results obtained cannot logically be attributed to differences in the proteins. It appears, then, that the factor responsible for the development of atherosclerosis is a nonprotein constituent of these animal foods. The diet used by Newburgh and Squier, which contained milk and casein, may well have contained enough cholesterol to account for the vascular lesions observed.⁹ It must be remembered, however, that Clarkson and

⁹ In order to determine whether this was true, my colleagues and I wished to give a diet rich in casein and sterol free and observe whether atherosclerosis would result. We were unsuccessful in completely freeing casein of sterol by any method of extraction. It could be rendered very poor in sterol, however, by repeatedly extracting it in hot alcohol according to the method of Randles and Knudson (*Studies on Cholesterol Synthesis of Cholesterol in Animal Body*, *J Biol Chem* **66** 459, 1925). A diet was made up consisting of 40 per cent of this extracted casein and 60 per cent sucrose, supplemented by carotene, ether-extracted yeast extract and linoleic acid. Unfortunately, the rabbits would not eat this diet.

Newbough showed that their beef muscle diets contained too little cholesterol to cause atherosclerosis. It appears, therefore, that there is a nonprotein constituent other than cholesterol in animal flesh which when ingested in sufficient quantities by rabbits causes hypercholesteremia and atherosclerosis. Further investigative studies of this problem are planned.

CONCLUSIONS

Diets containing 33 and 37.8 per cent of vegetable protein fed to rabbits for as long as eleven months failed to produce atherosclerosis.

Rarely were cholesterol values of the blood observed which were higher than the normal range. These were in every case associated with undernutrition and are thought not to result directly from ingestion of large quantities of vegetable protein.

These data suggest that the atherosclerosis observed when rabbits were fed diets rich in muscle meat was due to a nonprotein constituent of this animal food.

TORULA INFECTION OF THE CENTRAL NERVOUS SYSTEM

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Torula infection of the central nervous system is a rare disease but one which is of interest to the internist and the syphilologist as well as the neurologist. Clinically, in these cases a diagnosis of tumor or abscess of the brain, tuberculous meningitis, encephalitis or dementia paralytica is made, and frequently the true etiology is not revealed until autopsy is performed.

Rusk, in 1912, under the title "Systemic Oridiomycosis," was the first in this country to report a case of torula infection of the central nervous system. His report was antedated in Germany, however, by that of von Hansemann in 1905 and that of Turk in 1907, each of whom reported one case. It remained for Stoddard and Cutler in 1916 to describe the clinical characteristics of this disease and to isolate the causative organism by cultural methods, animal inoculations and histologic sections. They differentiated this condition from other mycotic infections of the central nervous system and named the organism *Torula histolytica*. They analyzed the previously reported cases and added reports of two of their own cases. By 1919 only thirteen instances of cerebral torulosis had been reported. Freeman and Weidman in 1923 gave a critical analysis of the cultural characteristics and classification of *Torula*. Freeman later reviewed the gross and histopathologic changes observed in nineteen cases of torulosis and in 1931, in an exhaustive monograph, he collected the reports of forty-three cases. Since then fifteen more instances have been recorded, in addition to the two cited here, making a total of sixty cases of invasion of the central nervous system by *Torula* (table 1) reported in the literature.

REPORT OF CASES

CASE 1—A German aged 59, the superintendent of a foundry, was admitted to the medical service of the Cleveland City Hospital on Oct. 26, 1933. His illness began five and one-half years before his admission to the hospital, with headache, vomiting, blurring of the vision and weakness. During the six months after the onset of the illness he was hospitalized on four different occasions by

From the Department of Dermatology and Syphilology, Western Reserve University and the Cleveland City Hospital, Cleveland, service of Dr. Harold N. Cole.

TABLE 1—*Analysis of Sixty Cases of Cerebrospinal Torulosis*

Sex of patient	No. of Cases
Males	39
Females	20
Not stated	1
Age distribution in years	
Under 10	1
10 19	6
20 29	9
30 39	9
40 49	15
50 59	16
60 69	2
Not stated	2
Diagnosis made before culture or autopsy	
Tuberculous meningitis	10
Meningitis (unqualified)	5
Encephalitis	7
Tumor of brain	6
Abscess of brain	4
Dementia psychosis	5
Dementia paralytica	2
Miscellaneous	2
Not stated	19
Duration of illness in months	
0 1	3
1	6
2	10
3	9
4	8
5	3
6	3
7	1
8	2
9	1
10 12	1
13 24	3
25 36	5
37 48	0
49 60	0
61 72	1
Unknown	4
Organs involved, including central nervous system	
Lungs	9
Generalized	8*
Kidney	2
Spleen	1
Adrenal glands	1
Abdominal node	1
Peribronchial node	1
Tonsil	3
Subcutaneous tissue	2
Skin	5
Central nervous system only	30
When diagnosed	
Post mortem	23
Ante mortem	37
How diagnosed	
Antemortem cultures only	10
Biopsy of brain ante mortem	2
Postmortem histologic sections	22
Cultures and postmortem histologic sections	26

* In one case the lungs were not involved

various medical attendants. Despite extensive roentgenographic and laboratory investigation, the only findings were "300 cells in the spinal fluid, chiefly lymphocytes and some small monocytes of various sizes and staining depth. There was a positive reaction to the globulin test, and the colloidal gold curve suggested the presence of meningeal irritation. Guinea-pig inoculations gave negative results. The patient was discharged ambulatory, with a final diagnosis of meningitis unqualified." Except for an occasional remission, his condition grew progressively worse, and about one year prior to his entry to this hospital he was confined to his bed.

Physical examination revealed that the patient was apathetic and not acutely ill, showing evidence of a loss of weight. Except for moderate arteriosclerosis, weakness and general muscular atrophy, there were no definite findings. The fundi showed some grayish exudate covering the vessels as they emerged from the central portion of the nerve head as probable evidence of an old choked disk. The impression reported at that time was that the condition was tumor of the brain, cerebral thrombosis, tuberculous meningitis or cerebrospinal syphilis. Laboratory investigation, including culture of the spinal fluid, revealed no abnormality. Roentgenograms of the chest and skull showed no evidence of a pathologic process. Roentgenograms revealed the presence of destructive mastoiditis.

Dr. L. Karnosh, of the neurologic department, who was called in in consultation reported the following neurologic components: generalized hyperreflexia, with more lively reflexes on the right, absence of the superficial reflexes symmetrically, a strong Babinski reflex on the right, a reduction in the size of the right pupil, with fine nystagmus when the eyes were directed to the right, mild hypesthesia over the second and third divisions of the right trigeminal nerve, voluntary and mimetic movements of the right side of the face, due to weakness, some central deafness on the right, hemihypesthesia to all qualities of sensation on the left, astereognosis of the left hand, and a very unsteady gait, which was attributed to general weakness. Combined cisternal and lumbar puncture revealed a practically complete subarachnoid block. The initial manometric readings were 60 mm of water in the cisterna and 0 mm in the lumbar region. The Queckenstedt test showed a 20 mm rise in the pressure in the cisterna and only 2 mm in the lumbar region, while straining caused a 20 mm rise cisternally and a 10 mm rise in the lumbar region.

It was believed that "most of the patient's symptoms were due to a diffuse process about the brain stem, from the midbrain to the lower border of the pons. In coordinating such symptomatology with the findings in the spinal fluid and with the unusual character of the disease, it was assumed that the lesions were of a granulomatous type, and it was therefore suggested that the condition might be due to a blastomycotic infection." The patient was transferred to the dermatologic service for further investigation and mycologic study. Suitable methods of culture and animal inoculation established the diagnosis of torula invasion of the central nervous system.

During the patient's entire stay of four months in the hospital he was afebrile except for a brief period of fever six weeks after entry, due to the development of bilateral purulent otitis media. The headaches, vomiting, weakness and disorientation progressed, and he died on December 29, five and one-half years after the onset of the illness.

Laboratory Examination—The blood count showed hemoglobin, 80 per cent (Sahli), erythrocytes, 5,050,000, leukocytes, 9,700, and polymorphonuclears, 76 per cent. Chemical analysis of the blood showed sugar during fasting, 92 mg, cholesterol, 250 mg, urea nitrogen, 121 mg, total protein nitrogen, 1,000 mg,

nonprotein nitrogen, 31 mg , total protein, 6.05 mg , albumin, 3.41 mg , albumin-globulin ratio, 1.28, and chlorides, 402 mg per hundred cubic centimeters. The icteric index was 6. The Wassermann reaction of the blood was negative, and cultures of the blood, including cultures for *Torula*, were sterile.

Repeated lumbar puncture showed the spinal fluid to be slightly xanthochromic. The cell count varied from 75 to 280, with a predominance of lymphocytes. An occasional yeast cell could be seen. Chemical analysis of the fluid revealed that the sugar content was markedly decreased, varying from 7 to 15 mg per hundred cubic centimeters. The analysis also showed sodium chloride, 612 mg , non-



Fig 1 (case 1) —Photomicrograph (low power) of the choroid plexus, hematoxylin and eosin stain. Note the destruction of the normal architecture and the replacement of tissue by pseudocysts.

protein nitrogen, 22 mg , total nitrogen, 393 mg , and total protein, 2.32 Gm. The Wassermann reaction was negative, and the mastic curve showed an increase in the middle zone.

A complete autopsy was performed by Dr. H. S. Reichle, of the department of pathology. The final anatomic diagnosis was infectious granulomatosis (*T. histolytica*), with invasion of the meninges and brain, chronic leptomeningitis, with external and internal hydrocephalus, chronic purulent mastoiditis, pulmonary emphysema, severe anthracosis and bronchopneumonia in the lower lobes of both lungs.

Torula in pure culture was recovered from the spinal fluid beneath the pons. A careful cultural search did not reveal the organism in the tonsils, lungs, bronchi, spleen, liver, kidney, extradural or subdural spaces or mastoid processes. Cultures of the heart blood were sterile. Except for the brain and meninges, histologic sections of all the organs failed to reveal the presence of Torula.

CASE 2—A white man aged 41 was first seen by a physician in June 1933. He complained of headaches in the frontal region of four months' duration. Results of physical examination were essentially unimportant. The headaches became progressively worse, and four months later the patient was suffering from

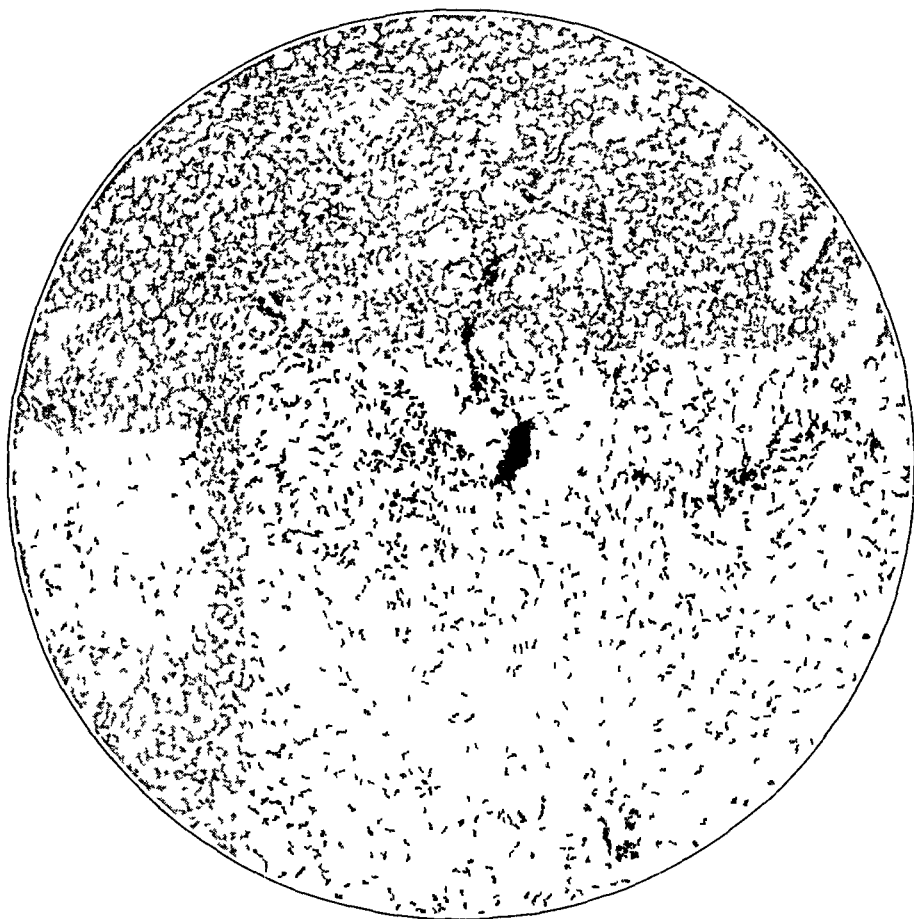


Fig. 2 (case 1)—Photomicrograph (moderate magnification) of the choroid plexus, hematoxylin and eosin stain. Note the granulomatous inflammatory reaction with lymphocytes, plasma cells and giant cells. The organisms can be seen as small, round bodies surrounded by a clear space or "lytic zone." Many of these spaces have coalesced, forming cystlike areas containing the organisms.

nausea, vomiting and dizziness. A Wassermann test of the blood was negative. Lumbar puncture revealed no abnormality, only 3 cells being seen. Ophthalmoscopic and otorhinolaryngologic investigations revealed nothing of significance. Roentgenograms of the chest and skull were negative, except for sclerosis of the left mastoid process and obliteration of the air cells. A neurologist who was called in consultation made a diagnosis of tumor of the frontal lobe of the brain.

The patient continued to suffer from headaches and vomiting. Three weeks' hospitalization in November 1933, nine months after the onset of the illness, revealed no definite physical findings, except evidence of an early stage of choked disk. The pressure of the cerebrospinal fluid was 300 mm. There were 160 cells, mostly lymphocytes. The Pandy test gave a positive result, with an atypical colloidal gold curve. The Wassermann reaction was negative.

For lack of any definite etiologic information and in view of the possibility that the condition might be due to syphilis of the central nervous system, anti-syphilitic therapy was instituted. Repeated spinal puncture alleviated the symp-

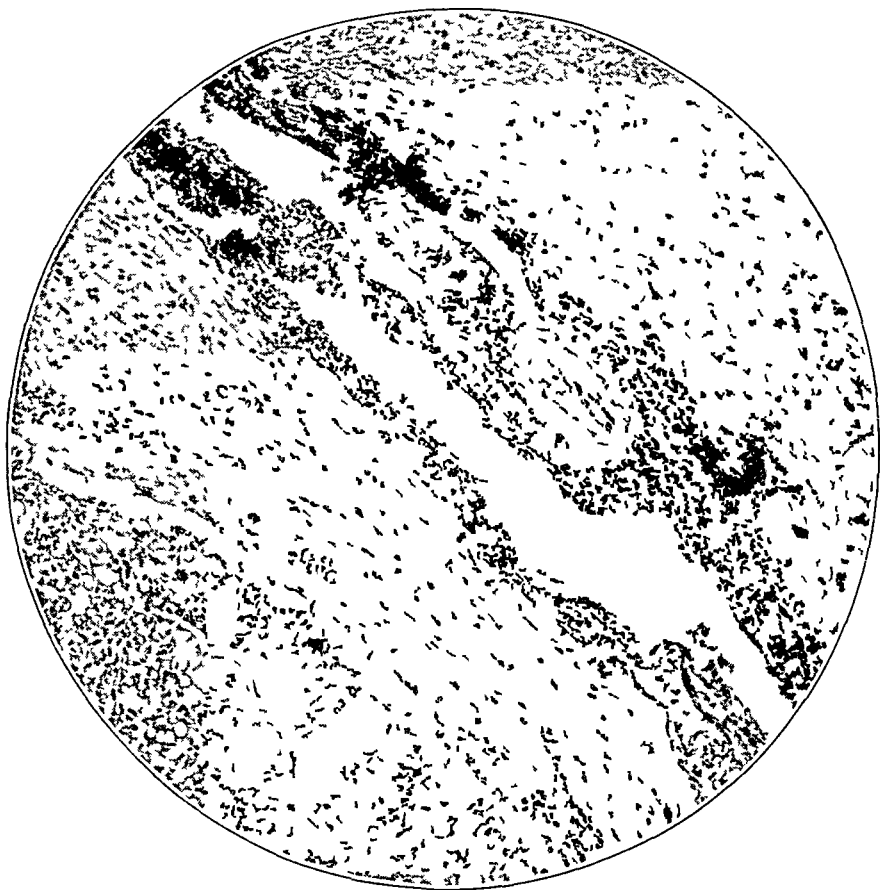


Fig. 3 (case 1) —Photomicrograph (moderate magnification) of a section of the brain, hematoxylin and eosin stain. Note the meningeal reaction about the pia-arachnoid of a cerebral sulcus, chiefly lymphocytes and plasma cells.

toms but revealed little variation from the findings of the earlier examinations. The eyegrounds were again examined, and it was decided to give the patient tryparsamide. He received five weekly injections, making a total of 9 Gm. Ten days after the last treatment rapid failure of vision resulted, with marked visual constriction. Headache and vomiting continued. An internist who was called in consultation favored the diagnosis of multiple sclerosis. In July 1934, seventeen months after the onset of the illness, because of the possibility of cerebral syphilis, the patient was referred to Dr. H. N. Cole, who made a tentative diagnosis of torulosis. The patient was hospitalized for lumbar puncture and further study.

The same procedure as in the first case established a definite diagnosis of torula infection of the central nervous system by means of cultural studies and animal inoculations

CLINICAL PICTURE AND DIAGNOSIS

The clinical manifestations of this disease are variable but can readily be understood when the increased intracranial pressure, the multiple granulomatous or cystic lesions and the involvement of the meninges are considered. The disease often sets in insidiously, with

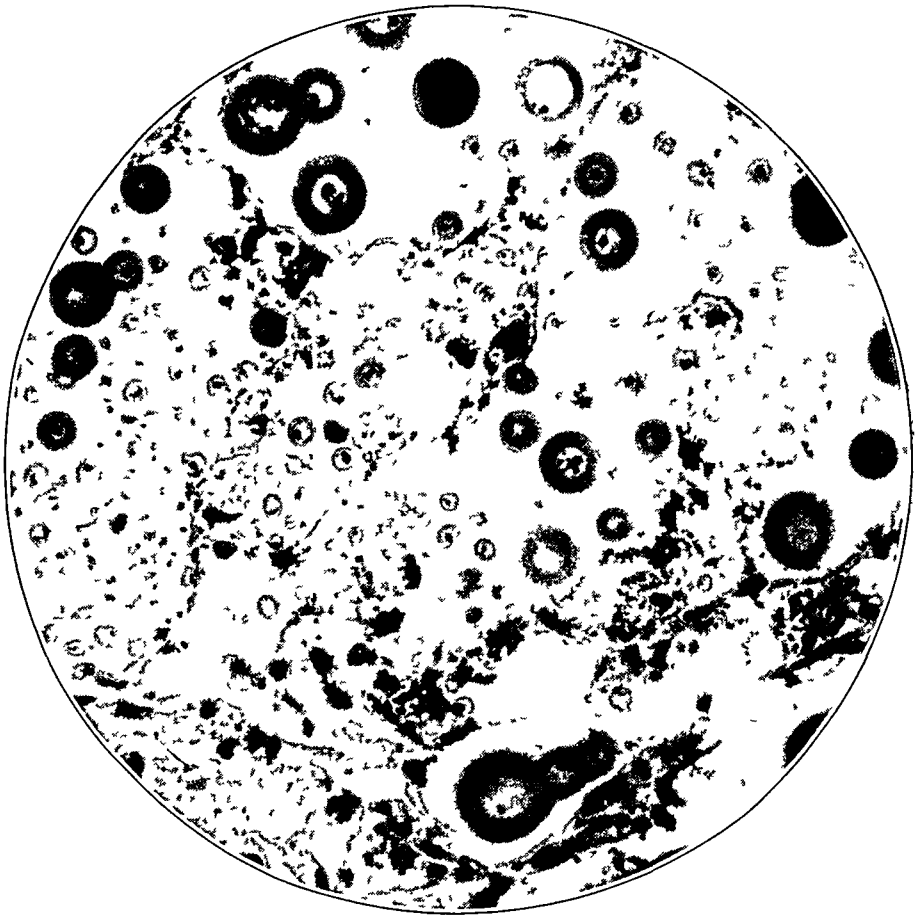


Fig 4—Photomicrograph (high power) of a section of the lung of a mouse, hematoxylin and eosin stain. The round, budding organisms are clearly shown. Note the variation in size, capsule formation, sharp margins, granules and lack of inflammatory reaction

intermittent severe headaches in the frontal region, later becoming more continuous, although occasionally the onset is violent and sudden, with excruciating headaches and vomiting. At times this cephalalgia may be the only clinical manifestation of the disease.

Dizziness, vertigo, stiffness and pain in the back of the neck are common symptoms. In many patients mental disorders are likely to occur, such as depression, disorientation, apathy, restlessness, irritability

and delirium Amblyopia is common Staggering, ataxia and hemiplegia have been noted The commonest physical finding is stiffness of the neck, the Kernig sign, as well as the Brudzinski sign The reflexes are variable The patellar and the achilles tendon reflex are usually lost Occasionally the Babinski sign is obtained Neuroretinitis, papilledema and choked disk are of frequent occurrence Other ocular disorders, such as strabismus, nystagmus and ptosis, as well as diplopia, also are noted

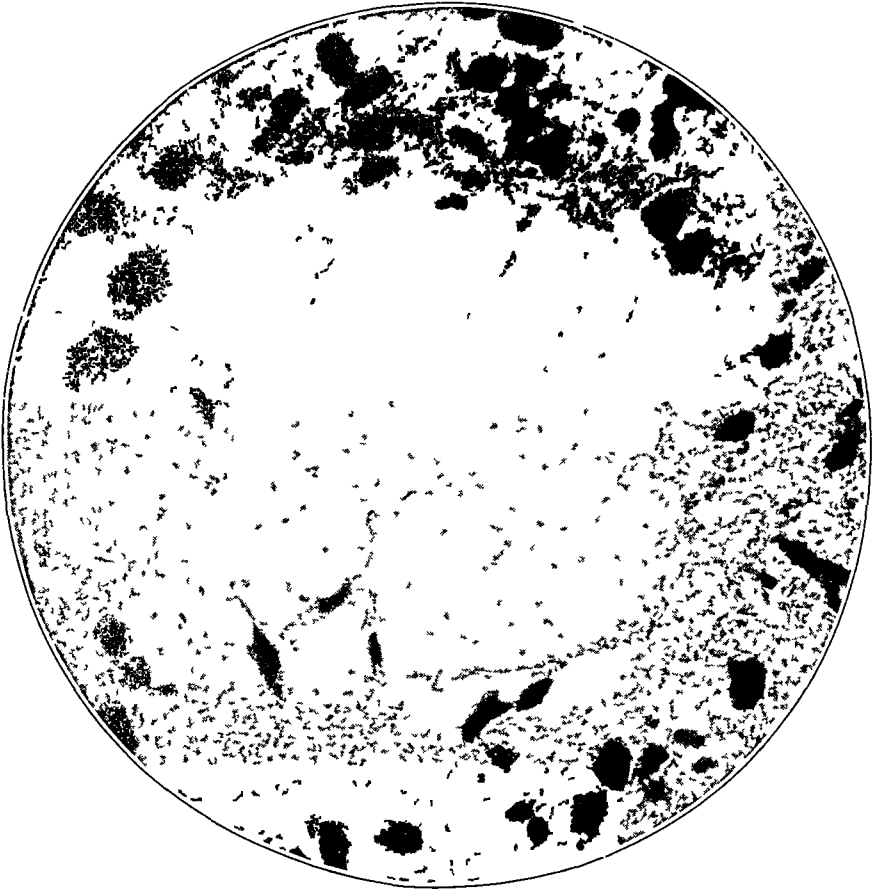


Fig 5—Photomicrograph (moderate magnification) of a section of the brain of a mouse, hematoxylin and eosin stain Note the cystic lesion containing *Torula* and remnants of brain tissue as thin trabeculations extending from the margins within the cyst

As a rule the patient is afebrile, and the symptoms of an acute infection are absent Rarely is the temperature over 101 F or the pulse rate over 100 The blood pressure remains normal As the disease progresses, loss of weight and strength invariably occurs The course is progressively downhill, although occasional periods of remission may be noted The patient ultimately becomes comatose and dies of respiratory failure

Torulosis of the central nervous system (table 1) is a disease of adult life, two thirds of the patients being between 30 and 60 years of age. The duration is variable, but in the majority of instances from one to six months of illness has been reported. Race, occupation and geography seem to be of no importance as regards incidence, for the disease has been noted in persons in all walks of life and in various parts of the globe. Males outnumber females two to one. A clinical diagnosis is most difficult because of the protean manifestations of this disease and its close simulation of more common conditions, particularly tuberculous meningitis, tumor or abscess of the brain and enceph-

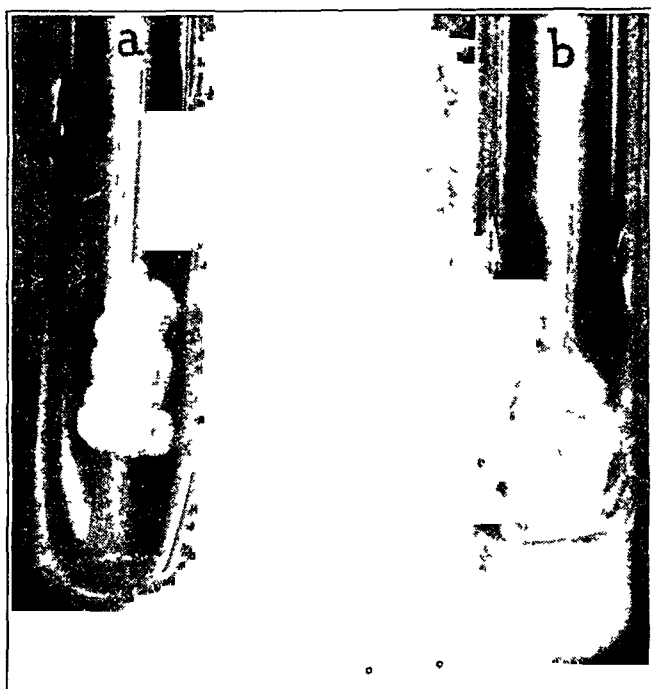


Fig 6—A month old culture of *Torula* from the second patient grown on Sabouraud's maltose agar medium (a). This shows the type of growth occasionally encountered—a moist, glistening, pasty, but rather firm growth which tends to form sectors about the periphery. A month old culture of *Torula* (courtesy of Dr. Weidman) grown on Sabouraud's maltose agar medium (b). This shows the typical mucoid, pasty, semifluid colony, with a major portion of the growth in the dependent portion of the tube.

alitis. Differentiation of torulosis from syphilis of the central nervous system is often necessary. However, the Wassermann reaction of the blood, the findings in the spinal fluid and/or a characteristic history invariably confirm the diagnosis in cases of syphilis. The differentiation of torulosis (table 2) from other mycotic infections of the central nervous system depends, of course, on cultures of the spinal fluid and perhaps on animal inoculation. In cases of cerebral involvement due to blastomycosis, coccidiosis, sporotrichosis or actinomycosis, invasion

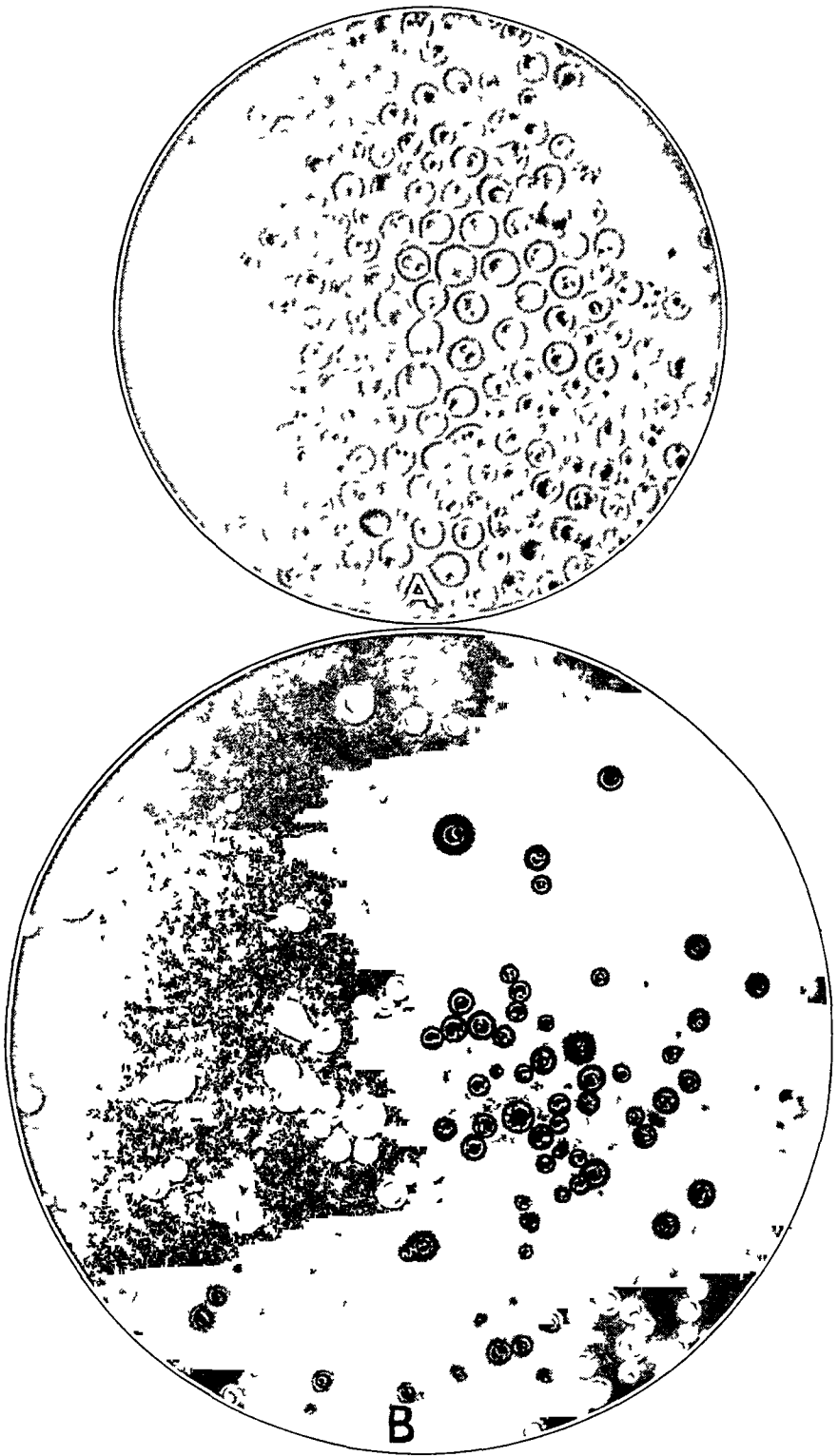


Fig 7—*A*, a hanging drop preparation of *Torula* in saline solution. Note the morphologic aspects and the various stages of budding. *B*, an india ink preparation of culture *a* shown in figure 6. The mucinoid envelop is seen as a clear zone or halo surrounding each organism.

TABLE 2—*Differential Features of Yeast, Monilia, Torula, Blastomyces and Coccidioides* ⁴

Genus	Synonyms or Name of Disease	Sugar Fermentation	Morphology in Lesions	Morphology in Culture	Cultural Characteristics	Animal Inoculation	Systems Involved	Pathologic Changes Produced
Saccharomyces	True yeasts	Strong	Oval and round budding cells, 5 to 15 microns in diameter, no mycelium (ascospores?)	Oval and round budding cells, 5 to 15 microns in diameter, no mycelium, ascospores present	Round, pasty, cream colored colonies	None	Skin, mild extent only	Abscess formation, with polymorphonuclear cells, necrosis and epithelial growth
Monilia	Oidium albicans	Moderate	Oval and round cells, 5 to 10 microns in diameter, mycelium usually present, no spores	Oval and round budding cells, 3 to 10 microns in diameter, mycelium usually present in old cultures, no spores	Round, pasty, glossy, raised, cream colored colonies, marginal fringe when mycelium is present	Rabbits, intraperitoneal	Mucous membrane, mouth, gastrointestinal tract, lungs, intertriginous portions of skin	Chronic ulceration
Torula	1 Wild yeast 2 Pseudo yeast 3 Cryptococcus hominis 4 European blastomycosis (Busse-Buschke disease)	Feeble	Encapsulated round and oval, budding, thick walled cells, usually 5 to 8 microns in diameter, occasionally 2 to 4 microns, no spores, no mycelium	Round and oval budding capsulated cells, 4 to 6 microns in diameter, no spores, no mycelium	At first, cream colored, later yellow to brown smooth, moist, mucoid colony	White mice and rats intraperitoneal or intracerebral	Central nervous system chiefly lung, viscera and skin to a lesser extent	Gelatinous yeast tumors, with slight inflammatory reaction, marked endothelial hyperplasia, foreign body giant cells, cysts in brain and occasional caseation
Blastomyces	1 Blastomyces dermatitidis 2 Oidiomyces 3 Oidium dermatitidis 4 Chicago disease 5 American blastomycosis	None	Round, budding, thick walled cells, 8 to 20 microns in diameter, no capsules, no spores, no mycelium	Mycelial growth, conidia and chlamydo spores in raquet mycelium	Smooth, grayish growth, later aerial mycelium, white to tin, downy or fluffy colony, radial folds and concentric rings, sometimes spiny growth	White mice and rats, intraperitoneal or intratesticular	Skin always, often bones, lungs, viscera and central nervous system	Miliary abscesses, connective tissue overgrowth, caseation, necrosis, epithelial hyperplasia, tubercular nodules and ulcers, polymorphonuclears present, not gelatinous
Coccidioides immitis	1 Coccidioidal granuloma 2 Californian disease	None	Round, thick walled cells, 5 to 7.5 microns in diameter, endospore formation, surface of cells often spiny, no budding, no mycelium	Mycelial growth, no conidia, intercalary chlamydospores in raquet mycelium	Smooth, grayish growth, later grayish white fluffy growth, occasionally spiny growth	Guinea pigs, intraperitoneal	All organs, including central nervous system, skin often	Chronic granulomas with abscess formation, necrosis ulceration, giant cells, fibrosis and erosion due to endothelial hyperplasia

Compiled after various authors (Freeman, 1931, Henneel, Weidman, Benham)

of the nervous system is usually secondary to primary involvement elsewhere, particularly in the skin or subcutaneous tissue

LABORATORY EXAMINATION

The routine laboratory examination of the blood and urine offers little as an aid in making a differential diagnosis. Mild anemia may be present, the leukocyte count is variable and there is no eosinophilia. Studies of the blood chemistry show no significant findings.

The examination of the spinal fluid, however, is most important. The fluid is clear, xanthochromic or turbid and under increased pressure. The cell count is increased, usually ranging from 200 to 800 cells, but there may be as few as 3 or as many as 1,000 cells. In many cases a pellicle forms. The specific gravity is usually about 1.008, and there is an increase in the albumin and globulin contents. The sugar content is variable but may be markedly decreased. The colloidal gold curve is not constant but is most often typical of meningitis or syphilis. The Wassermann reaction is negative.

Routine examination of the spinal fluid for a cell count in the counting chamber or a hanging drop preparation of the sediment from a centrifugated specimen may reveal the presence of the yeastlike cells, and even budding may be noted. A smear from this sediment may show round or oval, although somewhat distorted, gram-positive cells. A Wright stain (Jacobson) will help to distinguish lymphocytes from torulas, as the latter are not differentiated by this stain. If a loopful of the sediment is mixed with a drop of India ink on a slide and a coverslip is applied, the yeastlike organisms will appear to be surrounded by a halo and will stand out sharply against the black background. Microscopic examination alone, however, is inconclusive, and for a positive diagnosis culture and animal inoculation are essential.

ETIOLOGY

Torula is an oval or round, double-contoured, highly refractive yeastlike organism which reproduces both in tissue and in culture mediums only by budding. Sporulation and the formation of hyphae do not occur. It is widely distributed in nature and has been cultivated from plants and the bodies of many insects, as well as from canned butter (Henrici) and milk. It is ordinarily nonpathogenic. Various saprophytic or avirulent strains have been recovered also from normal skin (Benham and Hopkins), from the throat¹ and from the gastro-intestinal tract of man (Anderson).

Certain strains, however, have pathogenic properties (Benham) and become parasitic on man. Cases of torulosis in animals also have been

¹ Tanner and Lampert. Tanner, Lampert and Lampert.

reported² The portal of entry is not known, but the organisms gain entrance most likely by way of the upper respiratory tract to the lung and the central nervous system While Torula has a special predilection for nerve tissue, generalization may occur Rarely, the lungs only may be involved³ At times localized abscesses⁴ and cutaneous lesions in conjunction with cerebral involvement⁵ have been noted However, nonfatal localized lesions without cerebral involvement also have been reported⁶ In some instances the relation of Hodgkin's disease to torulosis has been demonstrated⁷

An antemortem diagnosis can be made only by direct examination of the spinal fluid, corroborated by cultural studies and animal inoculations Repeated examination of the spinal fluid may be necessary, as at times the organisms may be few Centrifugation and examination of the sediment will assist materially

Torula appears to grow readily on the ordinary bacteriologic mediums, although an acid medium, such as Sabouraud's maltose agar, favors a more rapid growth Sufficient time, however, should be allowed for the colonies to appear The tubes should not be discarded for at least ten days The cultures grow equally well at room temperature and in the incubator Fresh spinal fluid is not a requisite, as the organisms are resistant The colonies first appear as minute, elevated, whitish, circular, glistening dots with well defined margins They grow slowly and are of a moist and pasty consistency, so that they tend to slide down the slant to the dependent portion of the tube Primary cultures usually appear within four or five days, although subsequent transplants grow much more rapidly The cultures tend to become yellowish brown with age Young cultures are gram-positive, while older cultures are gram-negative

In broth the growth collects in the bottom in a compact mass without turbidity of the medium Microscopic cultures or a hanging drop preparation from a gross culture will not show any spore formation or hyphae In one month old colonies an india ink preparation (Weidman and Freeman) will show the organism's most characteristic feature—a clear zone or halo surrounding each cell The ability of this organism to ferment sugars is very feeble (Weidman)

For animal inoculation, white mice are best One cubic centimeter of the organisms suspended in saline solution is injected intraperito-

2 Frothingham Weidman and Ratcliffe

3 Sheppe Hardaway and Crawford

4 Smith and Crawford Johns and Attaway

5 Verse Rappaport and Kaplan Urbach and Zach Bernhardt, Zalewski and Burawski Mook and Moore Weidman (1933) Wile

6 Gill McGhee and Michelson Berghausen Jones

7 Cabot Fitchett and Weidman

neally The mice usually succumb to the infection within a month If they do not, they should be killed, and cultures should be made from specimens obtained from the brain, liver, kidney, lung and spleen Histologic sections will usually substantiate the cultural findings Post-mortem examination of the mice rarely reveals any gross pathologic change, despite extensive microscopic involvement, although occasionally cystic or nodular lesions the size of a pinhead can be seen

In the tissues the organisms vary from minute, round objects, only a few microns in diameter, to large, round bodies, from 40 to 50 microns in diameter The shape may be spherical or oval The margin is rather sharp, and the larger cells frequently have a double contour The formation of a capsule is not constant The organism is variable in its reaction to stains With hematoxylin and eosin stain they become slightly bluish or at times pink, or they may take no stain whatever, appearing as clear refractile bodies With the Gram stain they show marked amphophilia, so that many of the organisms are intensely purple or even black while others take on a delicate shade of pink Minute granules can often be seen within the bodies of these cells In tissue, as in culture, reproduction is only by budding

PATHOLOGIC PICTURE

According to the gross pathologic pictures the various forms of this disease have been classified by Freeman (1930 and 1931) into three types (1) a purely meningeal form, with diffuse or granulomatous meningitis, (2) a perivascular form, with small granulomas or cysts in the cortex, extending from the surface of the brain along the course of the vessels into the cerebral parenchyma, and (3) an embolic form, with deeply placed lesions lying chiefly in the gray matter of the basal ganglions but occasionally in the white matter of both the cerebellum and the cerebrum

TREATMENT

There is no specific treatment for this disease—all proved cases have been fatal Some relief may be obtained by repeated spinal puncture to alleviate the symptoms due to the increased intracranial pressure

COMMENT

The first case reported was unusual in that the duration of the disease was prolonged An illness of five and one-half years is the longest on record (the longest duration previously reported [Urbach and Zach] was two and one-half years) Despite this prolonged period of infection the cerebral invasion was well localized to the meninges and choroid plexus, and general invasion did not take place by way of the ventricular system or the meninges The early finding of "300

cells in the spinal fluid, with many small monocytes of various sizes and staining depth," strongly suggests that *Torula* was present then but not recognized, despite cultures and guinea-pig inoculation

In many other cases reported the specimens of cerebrospinal fluid which were sent for culture were said to be sterile. This may have been due to the following facts. First, the laboratory technician may not have been familiar with this organism. Second, only minute amounts of the fluid may have been used on or in the culture mediums. Third, even under optimum conditions it may be four days at the earliest before a small colony the size of a pinpoint makes its appearance. Most cultures made as a routine will have been discarded by then and reported as sterile or showing no growth. Fourth, only ordinary culture mediums may have been used. In cases of suspected torulosis sugar containing mediums which favor a more rapid growth likewise should be employed. Into the tube of Sabouraud's agar slant or broth 2 cc. of spinal fluid may be introduced and all inoculations may be made directly from the puncture needle, so as to insure the injection of a sufficient amount of material and to prevent the possibility of contamination. This will also prevent attributing the yeastlike colonies which may be obtained on cultivation to contaminants.

SUMMARY

Torula infection of the central nervous system is a chronic disease with clinical manifestations resembling those of tuberculous meningitis, tumor or abscess of the brain or encephalitis caused by a yeastlike budding organism, *Torula*. This organism is widely distributed in nature and is ordinarily nonpathogenic. It is distinguished from other similar organisms by the absence of mycelia and spore formation, the presence of a capsule and little tendency to ferment sugars. Certain strains, however, have pathogenic properties and manifest a special predilection for the central nervous system.

The disease sets in insidiously with persistent severe headache, stiffness of the neck and vomiting, and later dimness of vision or actual blindness, paralysis and convulsions may occur. As a rule the patient is afebrile, and the symptoms of an acute infection are absent. Stiffness of the neck, neuroretinitis or choked disks, diplopia, nystagmus, strabismus and variable changes in the reflexes are the outstanding physical findings. The blood count and blood chemistry reveal no characteristic picture. The spinal fluid is under increased pressure and is clear or xanthochromic, with an increased number of cells, chiefly lymphocytes, and an increase in the amount of albumin and of globulin. The colloidal gold curve is most often of a meningitic type. The diagnosis can be made ante mortem only by the identification of the causative organism in the spinal fluid. There is no effective treatment, the course

of the disease being steadily downward, with a fatal termination. Pathologically there is noted granulomatous meningitis, and if the cerebral tissue is involved, cystic and granulomatous lesions are present, with relatively slight inflammatory reaction.

Torulosis of the central nervous system is relatively easy to recognize, if it is kept in mind and if a diligent search is made in the spinal fluid for the causative organism. It should be considered as a possibility in cases of obscure cerebrospinal disease, especially those characterized by severe headaches without a definite etiology.

Dr Harold N. Cole gave many helpful suggestions during the preparation of this paper, and my colleagues at the Cleveland City Hospital assisted in various ways. Dr G. Y. Rusk, of the department of pathology, the Mount Zion Hospital, San Francisco, made the photomicrographs and reviewed the histologic sections. Dr Fred Weidman, of the department of dermatologic research, the University of Pennsylvania Medical School, permitted me to make a study in his laboratory of the various strains of *Torula*.

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UNUSUAL GLYCOGEN STORAGE IN A CASE OF DIABETES MELLITUS

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In fatal cases of diabetic acidosis the stores of glycogen in the body are, as a rule, markedly depleted. The importance of the case to be described lies in the paradoxical presence of an enlarged liver containing an excessive amount of glycogen in a diabetic patient who died in acidosis.

REPORT OF CASE

Clinical History—M R, a white man aged 24, was admitted to Duke Hospital on Nov 10, 1934, in severe diabetic acidosis. There was no family history of diabetes.

In February 1930, while at work in a college laboratory, he found that his urine gave a positive reaction for sugar. This was not confirmed by the physician of the college. In September 1930 the patient began to lose weight and to have polyuria, polyphagia and polydipsia. Two months later, while he was in the college infirmary for an unrelated cause, glycosuria was again detected. His family physician prescribed a diet with 15 units of insulin three times daily. The patient did not follow this regimen but soon fell into the habit of taking 20 or 30 units of insulin per day as he saw fit, covering each dose with a glass of orange juice.

On Feb 6 1931, he was admitted to Duke Hospital in moderate acidosis. There were signs of a considerable loss of weight and dehydration. He had an infection of the upper respiratory tract, and there was a furuncle over the right eye. No other abnormal physical findings were noted. The edge of the liver could not be palpated. It was recorded that the hepatic dulness extended for 11 cm above the right costal margin. At the time of the patient's admission to the hospital the sugar content of the blood was 480 mg per hundred cubic centimeters, carbon dioxide-combining power was 44.7 volumes per cent and the cholesterol content was 214 mg. Some difficulty was experienced in regulating the diabetes. However, after thirteen days his condition was considerably improved, and he was discharged on a diet of carbohydrate 100 Gm, protein 100 Gm and fat 200 Gm, with 30, 30 and 20 units of insulin per day.

In September 1933 the patient returned to the outpatient clinic, and urinalysis revealed a 4 plus reaction for sugar and a 2 plus reaction for diacetic acid. He admitted having difficulty in following his diet, which was then changed to carbohydrate 140 Gm, protein 70 Gm and fat 150 Gm per day.

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He was not heard from again until his final admission to the hospital. He had not kept to his diet, and for two or three months he had felt that the diabetes was becoming worse. He was losing weight and taking larger doses of insulin. On the rare occasions when he examined his urine it invariably gave a 4 plus reaction for sugar.

Six days before his final admission to the hospital he had what appeared to be a digestive upset, with nausea, vomiting and abdominal cramps. In spite of weakness, dyspnea and fatigue, he continued to work, and he was finally brought to the hospital in profound acidosis, with circulatory collapse bordering on a state of shock. He was in severe respiratory distress and was markedly dehydrated and stuporous. The edge of the liver was palpable 8 cm below the right costal margin. No other significant physical findings were noted.

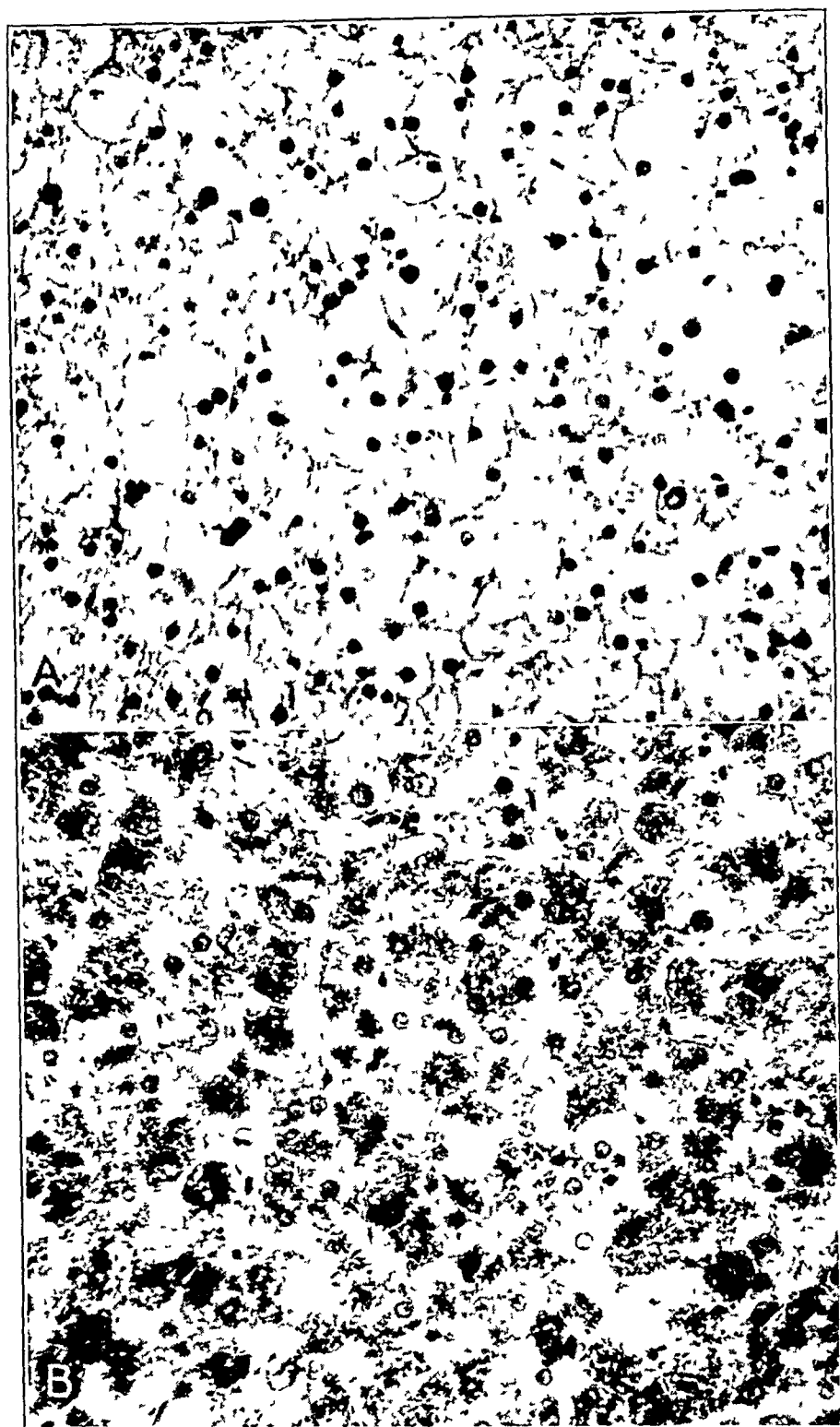
The urine contained 5 per cent sugar and large amounts of ketones. The carbon dioxide-combining power of the plasma was 17.4 volumes per cent. The sugar content of the blood ten hours after the patient's admission to the hospital was 320 mg per hundred cubic centimeters. In spite of the administration of insulin and caffeine and of fluids and dextrose intravenously, the patient died twelve hours after entry.

Gross Postmortem Examination (Nine Hours After Death)—The liver extended 9 cm below the right costal margin and weighed 2,700 Gm. The surface was smooth. The cut surface was waxy yellow and swollen. Each of the kidneys weighed 220 Gm and had a smooth surface. On the cut surface pronounced yellow striations were noted in the region of Henle's loop. The heart weighed 250 Gm and showed no hypertrophy or dilatation. The valves appeared normal. The pancreas weighed 100 Gm and showed no gross abnormality. The adrenal and thyroid glands showed normal size and consistency. Permission to open the cranial cavity was not granted.

Microscopic Postmortem Examination—The hepatic cells were greatly enlarged, and the cell membranes were fairly well outlined with eosin (fig. A). The cytoplasm was packed with fine granules. Some of the nuclei were enlarged and had a ringlike appearance. A few of the hepatic cells immediately surrounding the central veins were vacuolated. There was no congestion, cirrhosis or hemochromatosis. In the kidneys the epithelial cells of the loops of Henle were large, pale and vacuolated. There was also slight vacuolation of the epithelium of a few convoluted and collecting tubules. There was no vacuolation of the muscle fibers of the heart or voluntary muscle. The islands of Langerhans and the adrenal and thyroid glands appeared normal.

Pieces of liver, kidney and myocardium, after being left in a dilute solution of formaldehyde U S P (1:10) for two months were dehydrated with absolute alcohol, mounted in pyroxylin and stained with Best's carmine for glycogen. The great distention of the hepatic cells was due to the presence of large amounts of glycogen within the cytoplasm (fig. B). The cells nearest the central veins contained somewhat less glycogen than those nearer the portal areas. There was also some glycogen in the ringlike nuclei. The vacuolated epithelium in the loops of Henle of the kidney contained large amounts of glycogen, and the epithelium of the convoluted and collecting tubules contained smaller amounts. The myocardium contained no glycogen. After the tissues had been preserved in a modified Kaiserling no. 3 solution¹ for eighteen months, more sections were taken, dehydrated

1 An aqueous solution of sodium acetate 1 per cent, glycerin, 2 per cent, and a dilute solution of formaldehyde U S P (1:100).



A, photomicrograph of a section of the liver. The granules of glycogen in the cytoplasm have been dissolved out, giving the cells a vacuolated appearance. Hematoxylin and eosin stain. *B*, hepatic cells packed with many fine granules of glycogen. Best's carmine stain.

with absolute alcohol and mounted and stained for glycogen as before. The liver and kidneys still contained large amounts of glycogen, although the quantity appeared reduced.

Frozen sections of heart, liver and kidneys from formaldehyde-fixed tissues were stained with scarlet red and hematoxylin. The hepatic cells immediately surrounding the central veins contained small amounts of fat. The heart and kidneys contained no fat.

Anatomic Diagnosis—The diagnosis was hepatomegaly and abnormal storage of glycogen in the liver and kidneys (history of severe diabetes mellitus and death in acidosis).

Chemical Studies—When examined two months after autopsy the preserving fluid appeared milky. A qualitative test for glycogen by the iodine method was strongly positive. On the addition of 95 per cent alcohol to the fluid a white precipitate resulted. After acid hydrolysis of the precipitate a positive reaction to the Benedict test was obtained. With phenylhydrazine, typical dextrosazone crystals were formed.

After eighteen months in the Kaiserling solution portions from different areas of the liver were taken for the determination of the glycogen content by the method of Good, Kramer and Somogyi.² The average of six determinations was 3.18 per cent, with a variation between 3.09 and 3.56 per cent. The fluid content varied between 71 and 72 per cent, averaging 71.6 per cent. Hence, the average glycogen content per hundred grams of dry liver was 11.2 Gm. The glycogen content of the kidney was 0.22 per cent for wet tissue, or 0.76 per cent for dry tissue.

COMMENT

The usual postmortem observations on patients with untreated diabetic coma include an increased deposition of glycogen in the nuclei of the hepatic cells, in the heart muscle and in the convoluted tubules of the kidney, with depletion of glycogen in the skeletal muscle, skin and cytoplasm of the hepatic cells.³

Our patient had severe diabetes and died in acidosis, yet large amounts of glycogen were demonstrated in the cytoplasm of the hepatic cells and the liver was enlarged. Moderate amounts were present in the nuclei of the hepatic cells and in the tubular epithelium of the kidneys, none was present in the skeletal muscle or myocardium.

The increase in the size of the liver in diabetes has been ascribed to infiltration of fat, cirrhosis and chronic passive congestion. In our patient the enlargement must have been due to a massive deposition of glycogen in the hepatic cells. Unfortunately, the available data are insufficient to enable us definitely to explain the presence of the excessive amount of glycogen in the liver, although two lines of reasoning are open.

2 Good, C. A., Kramer, H., and Somogyi, M. The Determination of Glycogen, *J Biol Chem* **100** 485, 1933.

3 Warren, Shields. The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1930.

There is the possibility that our patient had glycogen storage disease (von Gierke⁴) and survived to young adulthood, when diabetes developed. Von Gierke's disease has been described as occurring in infancy and childhood and is characterized by early enlargement of the abdomen, due to storage of excessive amounts of glycogen, with marked hepatomegaly. The glycogen is remarkably stable, as shown by its slow response to epinephrine and in the delayed postmortem glycogenolysis.⁵ The heart and kidney, too, may be the sites of storage of glycogen.⁶ Also characteristic are hypoglycemia with ketosis during fasting, a flat, prolonged dextrose tolerance curve and unusual sensitivity to insulin. Tests of this nature had, of course, never been made in this case.

Parnas and Wagner⁷ reported a case which, in the light of our present knowledge, was probably one of glycogen storage disease in which diabetes developed. Gjurić⁸ recently reported two cases in females that fall into this category, one patient being aged 12 and the other 25. These patients at the time of the report required only small doses of insulin.

In our case there was no childhood history of abdominal enlargement, and hepatomegaly was not noted at the time of the patient's first admission to the hospital. It is possible that hepatomegaly was missed, but this is rather unlikely, since the examiner recorded even the upper margin of hepatic dullness.

The presence of glycogen in the tubular epithelium of the kidney is of no assistance in the diagnosis of glycogen storage disease, because it is frequently present also in diabetes mellitus.

The second line of reasoning has to do with the effects of insulin on the deposition of glycogen in the liver. That the glycogen content can be raised to normal in the liver of a diabetic patient by the use of insulin is generally agreed,⁹ but that excessive amounts can so be

4 von Gierke, E. Hepato-Nephromegalia glykogenica, Beitr z path Anat u z allg Path **82** 497, 1929.

5 van Creveld, S. Investigations on Glycogen Disease, Arch Dis Childhood **9** 9, 1934.

6 Humphreys, E. A., and Kato, Katsuji. Glycogen-Storage Disease, Am J Path **10** 589, 1934.

7 Wagner, R., and Parnas, J. K. Ueber eine eigenartige Störung des Kohlenhydratstoffwechsels und ihre Beziehungen zum Diabetes mellitus, Ztschr f d ges exper Med **25** 361, 1921. Parnas, J. K., and Wagner, R. Beobachtungen über Zuckerneubildung, Biochem Ztschr **127** 55, 1922.

8 Gjurić, A. Glycogen Storage Disease in Diabetes Mellitus, Časop lék česk **74** 514 (May 10) 1935.

9 Joslin, E. P. The Treatment of Diabetes Mellitus ed 5 Philadelphia Lea & Febiger, 1935. Warren³

stored has not been proved Wilder, Allan, Power and Robertson¹⁰ reported that the 3,300 Gm liver of a patient with hyperinsulinism due to carcinoma of the islands of Langerhans contained 8.25 per cent glycogen. These observations indicate that the liver of a nondiabetic subject may store glycogen in excess under the influence of large amounts of insulin, here produced by the tumor and its metastases. In our case the history suggested that the amount of insulin taken, together with a diet high in carbohydrate, might have resulted in changes similar to those noted by Wilder and his associates. A survey of the other cases of spontaneous hypoglycemia that have been reported has revealed no record of enlargement of the liver. Hanssen¹¹ noted enlargement of the liver in a few young patients who had diabetes that was difficult to control and who had received large amounts of insulin. In these patients the size of the liver returned to normal after regulation with a diet lower in carbohydrate. Infiltration of the liver with fat was assumed to have caused the enlargement, but no biopsy data were given to confirm that point.

In our case the enlargement of the liver and the persistence of 3.18 per cent glycogen in the hepatic tissue after eighteen months in an aqueous preserving fluid (which had extracted a considerable quantity) suggest that an exceedingly large amount of glycogen must have been present at the time of death or that some type of hepatic fixation of glycogen was present. Unfortunately, the special clinical and post-mortem tests that might have confirmed or disproved the latter possibility were not carried out.

SUMMARY

Hepatomegaly associated with the storage of a large amount of glycogen was noted in a diabetic patient who died in acidosis. Two possible explanations for this unusual condition are considered: first, this was a case of glycogen storage disease (von Gierke) in a subject who had survived to young adulthood, when diabetes developed, and, second, the glycogen was stored in the liver under the influence of large doses of insulin plus a high intake of carbohydrate.

10 Wilder, R. M., Allan, F. N., Power, M. H., and Robertson, H. E. Carcinoma of the Islands of the Pancreas, *J. A. M. A.* **89**: 348 (July 30) 1927.

11 Hanssen, P. Enlargement of the Liver in Diabetes Mellitus, *J. A. M. A.* **106**: 914 (March 14) 1936.

CHLOROMA

REVIEW OF THE LITERATURE FROM 1926 TO 1936 AND REPORT OF THREE CASES

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CHICAGO

A chloroma is any tumor which has a green color in the fresh state. Lehndorff in 1910 tabulated the data for the seventy-three cases of chloroma which had been reported up to that time. In 1926 Brannan summarized seventy-four reports of cases which appeared from 1910 to 1926, of which fifty-six were definitely cases of chloroma, the others being dubious examples. This present report brings the literature of chloroma up to date. The "Quarterly Cumulative Index Medicus" lists sixty-six references to papers, purporting to describe about eighty cases. Thirteen of these articles were not available for study, and twelve of the indexed papers did not concern chloroma. Of the fifty-eight cases summarized in table 1 (including three reported here for the first time), forty-six were unquestionable, while in ten cases there was a complete clinical syndrome of cranio-orbital tumor with leukemia, but no autopsy or biopsy was made in which the color of the tumor was noted. In the other two cases there was the classic syndrome, with greenish tissue visible ante mortem, but no necropsy was made. To be strictly academic, then, the present tabulation adds forty-six cases to the one hundred and twenty nine already reported.

Lehndorff's study showed that in fifty-six cases the condition was considered to be of lymphoid origin and in seventeen of myeloid origin. Brannan stated that in forty-nine of the cases which he studied the origin was definitely myeloid. Burgess stated as his conviction that in all cases of chloroma the condition is of myeloid origin. Askanazy offered a similar view. Current textbooks vary as to the opinion given. MacCallum, Naegeli, Aschoff and Ewing have described both myeloid and lymphoid forms. Malloy, Karsner, Wells, Piney and Boyd have stated that the process is always myeloid, although Boyd said he was not convinced that the myeloblast is the responsible cell. In fifty of the cases considered in this paper the condition was said to be of myeloid origin, and in only five of the indubitable examples was it stated to be of lymphoid origin. The basis for this statement was always that the large mononuclear cells in the blood and in the tumors were called

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TABLE 1—Summary of Cases of Chloroma¹

Author	Age	Sex	Site of Lesion			Post mortem Study	Leuko cytes	Immature Cells		
			Skele ton	Lymph Nodes	Spleen			Nervous System	Type	Per Cent
Unquestionable Cases										
Mullen	9 yr	M	p	p	p	o	p	120,000	Myeloblasts	72.0
Rothschild	11 yr	M	o	o	o	p	p	6,000	Normal blood	
Blatt	3 yr	F	p	p	o	p	o	13,000	Myeloblasts	4.5
Clivio and Mascherpa	9 yr	M	p	o	o	p	p	6,000	Large mononuclears	48.0
Teer, case 4	1 mo	M	p	p	p	o	p	104,000	Lymphoblasts	80.0
Case 6	5 yr	M	p	p	p	o	p	34,300	Myeloblasts	97.0
Rufano	48 yr	M	p	o	o	p	p	1,160 38,000	"Blastic"	
Haintz	23 yr	M	p	o	p	p	p	14,500	Myeloblasts	30.0
Rosenblum and Lebedewa	14 yr	M	p	p	p	o	p	11,300	Myeloblasts	66.0
	18 yr	M	p	p	p	o	p	5,400	Myeloblasts	67.0
Seemann and Siewert	42 yr	M	p	p	p	o	p	15,000	Myeloblasts	5.0
									L eosinophils	49.0
Monger	16 yr	M	p	p	p	p	p	16,000	"Blasts"	30.0
Critchley and Greenfield	19 yr	M	p	p	p	p	p	229,000	Myeloblasts	50.0
	8 yr	M	p	p	o	p	p	15,700	Myeloblasts	3.0
Weil, Isch Weil and Bertrand	27 yr	F	p	o	p			97,200	Undifferentiated	
Reddick and Brandes	28 yr	M	o	o	o		p	18,700	Myeloblasts	33.0
de Asua	17 yr	F	o	o	p	o	p	49,000	Many "blasts"	57.0
Zeiss	12 yr	F	p	p	p	p	p	20,800	Lymphoblasts	
Gamble	7 yr	F	p	p	o	p	o	34,000	Myeloblasts	26.0
Bainforth and Edwards	19 yr	F	p	p	o	o	p	8,300	Normal blood	20.0
	39 yr	F	p	p	p	p	p	25,600	Primitive lymphocytes	20.0
	33 yr	M	p	o	o	o	p	34,000	Lymphoblasts	69.0
	4½ yr	M	o	p	p	p	p	132,000	Primitive cells	79.0
Ashby	9 yr	M	p	p	p	p	p	22,000	Myeloblasts	71.0
Ashby and Smith	2½ yr	M	p	o	o	p	p	14,200	Myeloblasts	59.0
Washburn	22 mo	M	p	o	o	o	o	18,000	Myeloblasts	2.0
Swanson	2 yr	F	p	p	p	p	o	76,000	Myelocytes	0.5
Allen	4½ yr	F	p	p	p	p	o	41,000	Myeloblasts	29.0
	30 yr	F	o	p	p	o	p	15,000	Myeloblasts	31.0
Derman and Hirschitz	11 yr	M	o	p	p	o	p	7,800	Monocytes	58.0
								5,000	Myeloblasts	68.0

Quinke	37 yr	M	p	o	p	o,000	Lymphoblasts	300
Hertz	11 yr	F	p	p	o	15,000	Large lymphocytes	200
Doub and Hartmann	17 yr	M	p	p	p	24,500	Myeloblasts	800
Strasser	58 yr	F	o	o	o	1,100 310	Myeloblasts	40
Cohen (1924)	4½ yr	M	p	o	o	3,600	Myeloblasts	10
Kandel	22 yr	F	o	o	o	1,200	Myeloblasts	100
	25 yr	M	o	p	p	209,000	Myeloblasts	200
Lecene	13 yr	F	o	p	p	36,100	Myeloblasts	50
Heiberg	23 yr	M	p	o	o		Normal blood	
	2 yr	M						
Krumbein	5 mo	M						
	3 yr	M	o	p	o			
	6 yr	M						
Castorina	14 yr	F	p	p	p	8,200	Metamyelocytes	40
Nasso	5 yr	F	p	p	o	1,680	Myelocytes	150
	6 yr	M	p	p	p			
Clinical Syndrome, Green Tissue Visible								
Levy and I an	3 yr	M	p	o	o	60,400	Myelocytes	920
Peruzzi	3½ yr	M	p	p	p	14,000	Metamyelocytes	20
Clinical Syndrome, No Biopsy								
Volpe	22 mo	M	p	p	p	11,000	Myeloblasts	280
Ashby and Smith	4 yr	M	p	o	o	27,600	Myeloblasts	24
Nasso	7 yr	M	p	p	p	17,500	Myeloblasts	50
	7 yr	M	p	o	p	6,250	Myelocytes	100
	9 yr	M	p	o	o	5,630	Myelocytes	10
Castana	15 mo	M	p	p	p	14,000	Myeloblasts	10
Castorina	10 mo	F	p	p	p	16,600	Myeloblasts	15
	2 yr	M	p	o	p	20,000	Monoblasts	100
Gerbasi	20 mo	F	p	o	p	17,160	Immature cells	50
Gandolfo	28 mo	F	p	p	p	21,800	Myeloblasts	15
							Hemocyto blasts	120

* p indicates present during life, and o indicates absent during life

lymphocytes or lymphoblasts and the reaction of the tissues for peroxidase (if studied) was negative

The clinical features of the cases reported were as protean as the histologic material was specific. The green tumor was observed invading all parts of the body, and the variety of the involvement was responsible for the diverse clinical symptoms. Two main clinical types occurred, however. One was the so-called classic syndrome, in which a rapidly growing orbital tumor in a child resulted in profound proptosis. Associated with this were varying degrees of cranial tumefaction, lymphadenopathy and grossly noticeable involvement of other bones. Rapidly increasing, intractable anemia was frequently noted, and many of the papers recorded erythrocyte counts of less than 1,500,000. Splenic enlargement was not frequent, and a hemorrhagic diathesis was rare. The other type tended to occur in older patients and consisted of a rapid

TABLE 2—*Summary of Data*

	Number of Cases
Males	38
Females	20
Over 18 years old	15
Less than 18 years old	43
Leukocytes less than 6,000	8
6,000 to 15,000	13
Over 15,000	31
Leukemic blood	50
Normal blood	3
Diagnosis of myeloid leukemia	50
Diagnosis of lymphoid leukemia	6

decline in the patient's strength, profound anemia, varying amounts of osseous pain and gross bony enlargement and usually enlargement of the lymph nodes and spleen. Eight patients had leukocyte counts of less than 6,000 and three (Strasser, Reitano, Kandel, case 1) showed leukopenia (less than 2,000 leukocytes). In these cases necrotizing angina, stomatitis with bleeding and cerebral hemorrhage, respectively, occurred.

The common clinical feature in all these cases was the leukemia, with the exception of three cases (Rothschild, Bamforth and Edwards, case 1, Lecene) in which the leukocyte count was reported as normal. The leukocyte count varied from 299,000 (Kandel, case 2) to 310 (Strasser), and in the majority of cases a diagnosis of myeloid leukemia was made. In general, the percentage of myeloblasts was about 50, with extremes of 0 and 97 per cent (Fee, case 4). One patient (Levy and Laff) had 92 per cent myelocytes and no myeloblasts, another was unique in displaying 49 per cent eosinophils (Seemann and Sajzewa) in the peripheral blood. Frequently the differential count was described as consisting of primitive cells, undifferentiated cells, hematogonium

and hemohistioblasts (Gandolfo) On the stained films the anemia was apparent, and many nucleated and young erythrocytes were seen Lecène's case was unusual the patient had a tumor of the humerus, which when excised was said to be a myelocytic chloroma The blood was normal The patient was given roentgen therapy, and he was living and well two years later Only one other patient survived for as long as that, Washburn's patient—a 22½ month old boy A green tumor diagnosed as a myelocytoma was excised from the skull, and another tumor in the femur was treated with roentgen rays The blood is reported as having been questionably leukemic before therapy was started and as becoming normal afterward This boy was living and well two and one-half years later The remainder of the patients died rather promptly, few surviving for eight months after the symptoms appeared

Many different terms were employed in describing these cases, but the majority of authors (the best usage) called the classic syndrome in children chloroma The older patients with classic myeloid leukemia clinically and green tumors at necropsy were designated as having chloroleukemia The leukemia was usually called acute myeloid or myeloblastic, although in ordinary usage the term acute is reserved for conditions in which the blood contains in excess of 90 per cent myeloblasts and which are of short duration Certainly, the brief duration of life in most of these cases of myeloid leukemia justifies a diagnosis of acute myeloid leukemia

Other laboratory studies were not relevant, except that only one author (Gandolfo) reported the presence of Bence-Jones' proteose in the urine, although many reported its absence The calcium and phosphorus contents of the serum were generally normal, and the phosphatase content was never determined Treatment was varied but was mostly supportive and symptomatic Several of the German writers reported injecting neoarsphenamine to no avail If roentgen therapy was used, the patient's condition generally became worse This is just what happens in acute myeloblastic leukemia, and the bad result in chloroma helps justify calling the leukemia acute in the absence of the usual hematologic criterion One patient (Kandel, case 2) was given roentgen therapy and died a month later, after a rapid decline The same happened in several other cases and was especially striking in one case (Doub and Hartmann), in which the leukocyte count fell from 24,500 (83 per cent myeloblasts) to 1,150 in two days

The roentgenologic examination yields variable results In young children the only finding may be a separation of the cranial sutures (Cohen, 1924) Periosteal elevation is probably the most common finding and may give either of two appearances It may be lamellated

and resemble scurvy or, if ossification is occurring, Ewing's tumor, or there may be radiating spicules of ossifying material perpendicular to the shaft, in which case it resembles osteogenic sarcoma. There may be simply a generalized osteoporosis, or there may be multiple punched-out, fuzzy or sharp osteolytic lesions (Bamforth and Edwards, Doub and Hartmann), usually in the diaphysis and in the skull, and then the resemblance to multiple myeloma or metastatic carcinoma is striking. Massive rarefactions have been described (Washburn). Allison, and Doub and Hartmann have given good descriptions of the roentgenographic picture. The rather high incidence of bony involvement, when looked for, is in striking contrast to the situation in myeloid leukemia, in which Claver reported but one example of an osseous lesion in a series of eighty-two patients. The same paper reports a 7 per cent incidence of osseous lesions in lymphoid leukemia. The lesions in either type are indistinguishable from those reported in chloroma, a fact emphasized by Clark.

The differential diagnosis varies with the clinical picture. In the classic cranio-orbital syndrome, without changes in the blood, other malignant growths of the orbit and cranium, Mikulicz' disease and osteomyelitis and abscess must be considered. Cohen (1934) reported a case of orbital lymphoma in a 65 year old man who had chronic lymphoid leukemia. The tumor was not green, and the course was slow. With roentgenographic evidence of bony involvement and no changes in the blood, the conditions referred to in the previous paragraph must be considered, as well as the essential xanthomatoses in which there is splenomegaly as well. The differentiation will eventually be histologic, multiple myeloma being composed of plasma cells and the other diseases showing specific lesions. If, however, a patient has myeloid leukemia and bony and orbital tumors the diagnosis of chloroma is probably correct.

Pathologically, when careful histologic studies are made with appropriate stains, the observations are specific. The tumors are either myeloblastomas or myelocytomas. Depending on which cell type predominates, the reaction for oxidase will be negative or positive (typical myeloblasts contain no specific granules to give the reaction for peroxidase). However almost any such tumor will have enough promyelocytes or myelocytes with typical granulations to make diagnosis possible with stains for peroxidase. These tumors are composed of large anaplastic-appearing cells, with little stroma, no reticulin and fair vascularity. There are seldom regions of erythroblastic activity, although biopsy of one tumor (Castana) was described as showing erythromyeloblastoma. Active invasion of surrounding structures is prominent. The tumor and infiltrations are directly continuous either with a subperiosteal

accumulation or with a metaplastic lymph node. This relation to bone is striking in the skull and in the thorax. In the skull, which is involved in 73 per cent of cases (Rothschild), the green mass is seen to be adherent to the sutures, growing over, under and into the dura, the paranasal sinuses and the orbit, and infiltrating the nerves, scalp, sclera, choroid (Cohen, 1924) and subcutaneous tissues. In the thorax there are almost always large sheets of tumor adherent to and growing from the under surface of the sternum, through the pleura, into muscles. In one case (Quincke) there was extension into the myocardium and almost complete stricture of the pulmonary artery with tumor tissue. Along the vertebral column a green tumor from the periosteum and the lymph nodes may invade the neural canal, nerves, erectores spinae muscles, fill the pelvis and infiltrate the ovaries. The bone marrow may or may not be green tinged and in general is not. It is usually hyperplastic, gelatinous and grayish and may be almost liquid. The histologic picture is typical of myeloid leukemia of an acute variety, with myeloblasts predominating. Lymph nodes show only infiltration, as does the spleen, the follicles in either cases showing no proliferation.

When the central nervous system is involved it is usually by pressure or by obliteration of the blood supply, with resulting necrosis. Plugs of myeloblasts and myelocytes have been described (Critchley and Greenfield) in the vessels of the cord, and perivascular cuffing when present is accomplished by similar cells. Discrete tumors in the neural tissues have not been described. The infundibulum and choroid plexuses of the ventricles were green and infiltrated in one of the cases described by Critchley and Greenfield, but extension into the white matter had not occurred. The invasion of the neural canal frequently produces transverse myelitis, and thrombosis of the arteries may cause extensive ischemic necrosis. Rothschild's patient showed signs of a focal cerebral lesion. When decompression was performed a green tumor was revealed. Krumbein's patient had mastoiditis and showed signs suggesting thrombosis of the lateral sinus and meningitis. Mastoidectomy disclosed green tumor in the cells, and autopsy revealed more in the cranial cavity. Sections frequently showed marked infiltration of the peripheral nerves, probably a potent source of the pain from which so many patients suffered.

The spleen and the liver rarely contain green tumor tissue, but the kidneys seldom fail to have it, diffusely or in nodules. The green tumor is generally located in the cortex. The pancreas usually escapes, as do the adrenal glands and the bladder. The ovaries are frequently grotesquely enlarged by the chloroma. Peyet's patches of the gastrointestinal tract are never reported as green. In all these organs the usual gray leukemic infiltration may be seen. The pathologic picture,

then, is that of true neoplasia in every respect, with the proliferating cells myeloblasts and myelocytes. The difference from ordinary leukemia is the tendency of the infiltrations to act as metastases do and spread locally and destructively. The type of invasion, except for its close relation to bones and its inevitable periosteal involvement, closely resembles grossly that seen in lymphosarcoma.

CASE 1—A 22 year old white woman, a student, of Swedish ancestry, was first seen in the medical clinic of the University of Chicago on March 3, 1933. Her

TABLE 3—*Blood Counts in Case 1*

Date, 1933	Hemoglobin, %	Erythrocytes	Leukocytes	Platelets
3/ 3	39	1,610,000	2,100	
3/20	32	1,630,000	3,400	176,000
3/21	28	1,580,000	1,000	160,000
3/22	30	1,400,000	1,600	120,000
3/23	36	1,580,000	1,280	
3/24	39	1,600,000	3,000	130,000
3/25	40	1,400,000	1,200	
3/27	30	1,480,000	1,280	108,000
3/28	32	1,520,000	1,800	
3/30	24	1,400,000	1,200	
3/31	24		1,080	116,000
4/ 1	22	1,280,000	900	112,000
4/ 2	20	1,180,000	1,200	22,000

TABLE 4—*Differential Leukocyte Counts in Case 1*

Date, 1933	Myelo- blasts	Pro- myelo- cytes	Myelo- cytes	Meta- myelo- cytes	Poly- morpho- nuclears	Lympho- cytes	Mono- cytes
3/ 3	39	1			12	42	6
3/20	38	2		3	12	45	
3/21	30	4			8	58	
3/22	40	2	1	6		50	1
3/23	30	3	1	1	10	55	
3/24	25	4	2	5	14	50	
3/25	20	6	3	4	10	57	
3/26	39	4	7	5		45	
3/27	35	2	2	2	8	50	1
3/30	30	2			12	54	2
3/31	34	6	5		20	30	5
4/ 1	26	6	4	2	27	27	2
4/ 2	22	10	7	8	17	34	3

complaints were of pallor and weakness for four months. Two months prior to her admission to the clinic she had been sick in bed for four weeks, with a sore throat, followed by pain in both legs and in the back and a low grade fever. In the month prior to her admission to the clinic she had been failing rapidly. The past history was otherwise noncontributory. The menses were normal, and the patient had never been pregnant. Physical examination showed marked pallor, no petechiae, a pulse rate of 100, a barely palpable liver and a small retinal hemorrhage. The blood pressure was 114 systolic and 70 diastolic. The blood counts are listed in tables 3 and 4. Hospitalization was advised but not accomplished until February 20, when the patient had become much sicker. On her admission to the hospital there were more retinal hemorrhages, and the pallor was more striking. The course in the hospital was rapidly downhill, with an increasing temperature, showers of petechial hemorrhages, vaginal bleeding, stomatitis and

amblyopia Treatment was supportive, including blood transfusions The patient died on April 3, approximately five months after the onset of the illness

Gross Postmortem Examination (by Dr P R Cannon)—The liver was of normal size, weighing 1,200 Gm It was flabby, and the capsular surfaces were smooth Cut surfaces were brown, with indistinct lobular markings There was no visible leukemic infiltration The spleen was firm and weighed 160 Gm It had a smooth purple capsular surface, with prominent follicles on the cut surface The lymphoid follicles of the gastro-intestinal tract were not enlarged The kidneys weighed 110 Gm each and contained no gross leukemic infiltration The ovaries were enlarged (8 by 7 by 4.5 cm), hyperemic and hemorrhagic and contained numerous cysts The cut surface showed that the organs were composed mainly of solid tissue the color of which was somewhat obscured by blood The abdominal periaortic lymph nodes were diffusely enlarged and brownish green These nodes extended up past the celiac axis In the retroperitoneal tissues contiguous to the broad ligaments, particularly on the left, were large greenish gray nodes The mesenteric lymph nodes were normal The lungs were contracted and pinkish gray, with small patches of greenish tissue adherent to the visceral pleura of each apex The heart was normal, as was also the skeletal musculature The bodies of the third and fourth lumbar vertebrae contained a slightly greenish, gelatinous bone marrow, and similar marrow was seen in the ribs and sternum Anteriorly, along each side of the vertebral column, greenish gray tissue was seen

Histologic Examination—The lymph nodes showed moderate hyperplasia of the reticular elements but not of the lymphoid follicles The spleen showed hyperplasia of the red pulp, with many histiocytes enlarged and prominent There was no conspicuous myelopoiesis, and the follicles were compact The ovaries were almost completely replaced by a growth of neoplastic mononuclear cells with pale nuclei, prominent nucleoli and nongranular cytoplasm There was no reticulin but much rhexis Mitotic figures were frequent These cells were identified as myeloblasts The pelvic fat was infiltrated with these tumor cells, as were the nerves and skeletal muscle, in which there was also necrosis The retroperitoneal (green) lymph nodes were completely replaced by tumor cells There were no leukemic foci in the liver or kidneys There was moderate hyperplasia of the lymphoid tissue in the intestines, and extension of the neoplastic tissue into the serosa was noted The bone marrow was markedly hyperplastic, with many myeloblasts, which were readily identifiable by comparison as the tumor cells The sections were characteristic of myeloid leukemia of an acute type

CASE 2—A 25 year old white man, of American ancestry, was first seen in the medical clinic of the University of Chicago on Aug 15, 1934 His complaints were of pain in the hips, swelling of the angles of the jaw and loss of 20 pounds (9 Kg) within the past six weeks His past and family histories were irrelevant On examination pronounced pallor and cervical lymphadenopathy were obvious The pulse rate was 108, the temperature 100 F and the blood pressure 130 systolic and 70 diastolic In the ocular fundi were hemorrhages and leukemic infiltration The liver was palpable and smooth, 5 cm below the margin of the ribs on the right The spleen was palpable 7 cm below the left ribs, neither the liver nor the spleen was tender A few small axillary and inguinal nodes could be felt Roentgenograms displayed small diffusely scattered infiltrative lesions in the apex of the left lung and subclavicular area The patient entered the Billings Hospital on August 17 for roentgen therapy because of enlargement of the spleen and leukocytosis (see tables 5 and 6 for the results of the blood counts) In the next seven days he received a total of 1,185 roentgen units over the cervical nodes, spleen and right hip He was discharged on August 27, feeling much better He was

seen on September 6 in the hematologic clinic. He was feeling stronger and was given solution of potassium arsenite. On September 13 the temperature was 102 F and the pulse rate 128, and the patient had a bad cold and cough. Rest in bed was ordered, but the cough became worse. He was readmitted to the hospital on September 19 in a moribund condition. He died the next day, approximately three months after the onset of symptoms.

Gross Postmortem Examination (by Dr E. Humphreys).—There was a moderate amount of blood-tinged fluid in the pleural and pericardial cavities. Numerous petechial hemorrhages and suggillations were seen in the parietal pericardium and the epicardium. The heart was flabby, and the foramen ovale was

TABLE 5—*Blood Counts in Case 2*

Date, 1934	Hemoglobin, %	Erythrocytes	Leukocytes	Platelets
8/16	51	2,530,000	276,000	260,000
8/17	48	2,980,000	248,000	
8/18	50	2,370,000	203,000	
8/19	46	2,040,000	121,000	
8/20	46	2,450,000	91,800	
8/21	48	2,430,000	115,000	
8/22	43	2,000,000	68,600	
8/23	52	2,650,000	79,000	
8/24	54	2,630,000	75,000	
8/25	50	2,410,000	47,800	
8/26	47	1,610,000	35,000	
8/27	51	2,450,000	31,000	50,000
8/28	49		23,200	
9/ 6	48	2,710,000	43,000	
9/13	44	2,377,000	113,000	
9/19	28	1,470,000	157,400	
9/20			299,000	

TABLE 6—*Differential Leukocyte Counts in Case 2*

Date, 1934	Myelo blasts	Pro myelo cytes	Myelo cytes	Meta myelo cytes	Poly morpho nuclears	Lympho cytes	Mono cytes
8/16	12	6	4	12	45	8	13
8/20	7	8	4	16	52	2	11
9/ 6	8	6	4	15	43	9	15
9/13	9	16	12	20	29	8	7
9/19	20	13	4	9	38	5	11
9/20	13	11	14	27	25	3	7

patent "Thrush breast" mottling of the endocardium and gray leukemic mottling of the myocardium were noted. The liver was large (2,250 Gm.) and firm, with no definite gross infiltration. The spleen was moderately firm and weighed 710 Gm. The cut surface was mottled brownish red. The gastro-intestinal tract displayed petechial hemorrhages and distinctly enlarged Peyer patches. The kidneys were large (290 and 220 Gm., respectively), and showed diffuse, nodular greenish infiltration of the cortex. This green tumor was estimated to replace fully 60 per cent of the cortex of one kidney. The lymph nodes were variable; the cervical nodes were not enlarged, while the tracheobronchial nodes were prominently enlarged and had a mottled gray-green cut surface, especially peripherally. The peripancreatic and periaortic and mesenteric nodes were enlarged and greenish. A blood clot from the portal vein was greenish red. The bodies of the lumbar vertebrae had marrow the color of which resembled that of the lymph nodes: greenish gray, with scarcely a tinge of pink. The marrow of the upper third of the femur was greenish gray, soft and abundant. The marrow of the ribs was scanty, semi-

liquid and greenish. When the periosteum was stripped from the sacrum, ribs and vertebral bodies a paper-thin layer of greenish tissue was seen loosely adherent to the bone.

Histologic Examination—The bone marrow was a solid tissue with few fat cells and was made up chiefly of myeloid tissue. The predominant recognizable cells were of the leukoblastic series, and immature forms were more numerous than mature cells. In many regions the predominant cells were myeloblasts. In many regions the proportion of eosinophils was high, and most of the cells were myelocytes. One striking feature was the absence of typical megakaryocytes from the marrow. The spleen was packed with cells of the type seen in the marrow, with a few small hemorrhages and numerous hemosiderin-filled phagocytes. The liver contained a few small leukemic infiltrations about and in the triads. The lymph nodes showed varying degrees of leukemic infiltration and obliteration of the architecture. In the kidneys there were leukemic infiltrations in the cortex and medulla, hilar fat and calices. The myocardium contained many small leukemic infiltrations about the larger blood vessels. In the right atrium was a massive hemorrhage disrupting the muscle fibers, which were degenerating. The lungs had small confluent bronchopneumonia-like nodules composed mostly of immature cells. In the submucosa of the appendix was marked leukemic infiltration.

CASE 3—This patient was a girl aged 13 years who had been under the care of Dr. Marie Ortmyer, of Chicago. In June 1930 the abdomen began to enlarge and in October the cervical lymph nodes became large. The girl became sicker and weaker and was admitted to the Women's and Children's Hospital on March 23, 1931. The blood count at that time was as follows: hemoglobin, 55 per cent, erythrocytes, 2,410,000, leukocytes, 24,000, myeloblasts, 5 per cent, promyelocytes, 9 per cent, myelocytes, 13 per cent, metamyelocytes, 18 per cent, polymorphonuclears, 40 per cent, basophils, 2 per cent, lymphocytes, 9 per cent, and monocytes, 3 per cent. The patient rapidly became worse, and transverse myelitis, pericardial effusion, cardiac decompensation and trophic ulcers developed successively. She died in April 1931. The last blood count, made on April 4, showed hemoglobin, 20 per cent, erythrocytes, 2,120,000, and leukocytes, 36,100. At autopsy green tumors were noted in the lymph nodes, ovaries, kidneys and bone marrow. The histologic diagnosis was acute myeloid leukemia. (This case will be reported in detail later by Dr. Ortmyer.)

These three cases are examples of the second type of chloromatous involvement, i. e., chloroleukemia. The diagnoses during life were, respectively, subacute myeloid leukemia with leukopenia, subacute myeloid leukemia and chronic myeloid leukemia. Green tumor tissue was found in all cases at autopsy, and histologically there was no question but that the process was a fairly acute myeloid leukemia. All the evidence gleaned from a study of the cases that have been reported favors the theory that chloroma is always associated with myeloid leukemia. In well studied cases of characteristic lymphosarcoma (Steinberg) and so-called leukosarcoma, which may be considered as lymphatic analogues of chloroma, green pigmentation has never been reported. Buigess said he felt that if the disease is ever of lymphoid origin, occasional cases in which there is a blood picture of chronic lymphoid leukemia (i. e., many small lymphocytes) should occur. This

is not unreasonable, for in the cases reported the blood picture varied all the way from profound neutropenia to that of the most acute myeloid leukemia. Cases have been reported in which the leukocyte count was as high as 1,880,000 (Burgess) and in which there were all the characteristics of chronic myeloid leukemia. Such a case as Burgess described has not been reported. In all the cases described as of lymphatic origin the blood contained large mononuclear cells, with nucleoli and irregular lobulated nuclei, called lymphoblasts, either because of their extrinsic appearance or because they did not show a reaction for peroxidase. It is admittedly difficult to differentiate isolated myeloblasts from lymphoblasts, and the stain for peroxidase is of no help, for neither type of cell has any granules (except the Auer bodies, which show a negative reaction for peroxidase). Only by clearly identifying less immature cells as of one series or another can this reaction be of value. The true distinction should be made from histologic preparations of the marrow and lymph nodes with appropriate stains for granules, such as the Maximow stain. In the cases described in which the condition was of lymphoid origin the description of the marrow and nodes was not specific and could not be considered as convincing.

The green pigment is a source of great interest. It is apparently a lipochrome and is said to contain iron. The one certain feature is that it disappears in about an hour but may be recalled with hydrogen peroxide. It is important to remember that no lymphoblastoma is ever green pigmented. The myeloid neoplasm of the common fowl (Mathews) called, curiously, leukochloroma, is not green and is composed solely of neoplastic myelocytes. On the other hand, green myelocytomas are reported in man. The pigment is ordinarily attributed to the myeloblasts and the eosinophils. The tumors of the patient with eosinophilic leukemia (Seemann and Sajzewa) were no greener than those of any other patient. In the three cases reported in detail in this paper no study was made of the pigment.

Discussions as to the significance of chloroma are plentiful in the literature. It is generally asserted that chloromas "prove" or suggest strongly the close relation, if not the identity, of myelogenous leukemia and neoplasms in general. The invasive feature of the chloroma is the point emphasized for the argument. It has never been apparent why the fact that myeloid cells in classic cases of leukemia do not erode bone is considered inferentially as evidence against the presence of a neoplasia. But such may be the case, for this fact is seized on in discussions of chloroma to demonstrate that myeloid cells (which are concomitantly causing leukemia and are capable of infiltrating the skin, heart and liver and of producing metaplasia in the lymph nodes and

spleen) are neoplastic. It should be apparent that the myeloid cells, specifically the multipotential myeloblasts, in chloroma simply assume another rôle and become capable of destructive invasion and of forming or cooperating in the forming of green tumors.

SUMMARY AND CONCLUSIONS

The literature on chloroma is reviewed from 1926 to the present, and three new cases are reported.

One hundred and seventy-five indubitable cases of chloroma have been reported in the world literature.

With recent improvements in staining technic and better differentiation of the acute lymphoid and myeloid leukemias, almost all the recent cases of chloroma have been reported as cases of myeloid leukemia, several standard texts to the contrary.

The inevitable association of chloroma with myeloid leukemia should make it obvious that chloroma is simply a variant of myeloid leukemia, with the multipotential myeloblast assuming the distinctive rôle as type cell of an invasive neoplasm.

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TREATMENT OF OCCLUSIVE ARTERIAL DISEASE OF THE EXTREMITIES BY PASSIVE VASCULAR EXERCISE

REPORT OF SIXTY-EIGHT CASES

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The old idea that the minute volume of blood flowing through distal parts of the body can be increased by lowering the pressure of the an in contact with these parts, which was first utilized therapeutically over a hundred years ago, has been revived again recently and, chiefly through the efforts of Louis G Herrmann, has been applied on a larger scale than ever before in the treatment of occlusive arterial disease of the extremities. The history of this method, illuminated by voluminous quotations and an exhaustive bibliography, the theory on which it is based and the modern technic of its application are given in Herrmann's¹ monograph, but many more data bearing on the results of its employment must be tabulated before its value and applicability can be ascertained exactly. It is to help satisfy that desideratum that this report² is presented.

METHOD

We planned to treat each affected extremity for one hundred hours, at the rate of five (consecutive) hours daily, by alternately raising and lowering the environmental pressure 20 and 80 mm of mercury, respectively, four times a minute, but it was often necessary to modify this program to comply with various exigencies. In some cases satisfactory results were obtained in less than one hundred hours, whereas in others it seemed advisable to continue the treatment much longer. The five hours per diem were not always consecutive hours. Occasionally treatment was omitted entirely for a day or two, and the individual periods of treatment were not infrequently short and irregularly spaced. In a few cases 2 ounces (60 cc) of whisky was given just before each period of treatment, but other forms of adjuvant treatment, such as local artificial hyperthermia, active vascular exercises and vasodilator drugs, were dispensed with as far as possible.

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1 Herrmann, Louis G. Passive Vascular Exercises, and the Conservative Management of Obliterative Arterial Diseases of the Extremities, Philadelphia, J B Lippincott Company, 1936

2 A preliminary report has appeared (J Iowa M Soc 25 549, 1935)

in order to allow an unobstructed view of the results of varying the environmental pressure. Ulcers were left undisturbed, except for a protective covering. Much difficulty was experienced with the crude rubber cuffs which were originally furnished with the pavaex boot. They were often uncomfortable, frequently they were so tight or so loose that effective treatment was impossible, and in many instances they were difficult to apply and remove.

In two years sixty-eight patients received a total of five thousand, nine hundred and forty-seven hours of treatment. There were thirty-nine cases of arteriosclerosis obliterans, eight of thrombo-angitis obliterans, twelve of sudden occlusion of a major artery and nine of miscellaneous disorders. The selection of cases was made purely on clinical grounds, without the employment of a special diagnostic procedure of any kind. Patients were accepted or rejected strictly on the merits in each case, but no patient was refused treatment simply because a good result seemed unlikely.

RESULTS

At the end of thirty hours of treatment it was often possible to predict what the final result would be. Rest pain was usually relieved during actual treatment, but frequently it recurred in the intervals between treatments and in a few cases seemed to be aggravated by the treatment. Cyanosis was lessened, as a rule. Occasionally, relief of pain resulted without an appreciable change in the degree of cyanosis. Intermittent claudication proved rather refractory. Partial relief was obtained often but complete relief rarely. Small chronic ulcers became less painful and tended to heal slowly. Neither frank gangrene nor complicating osteomyelitis was affected. The presence of even large varicose veins did not interfere with the treatment or its results. In patients who responded most favorably, sweating increased, the skin became pink, the temperature of the skin rose and pain and paresthesia disappeared. As it is important not to overrate a method which is still in the experimental stage, we have graded our results as conservatively and judiciously as possible.

Arteriosclerosis Obliterans—Tables 1, 2 and 3 present the essential data in this group of thirty-nine cases. Our policy at first was to test the method wholly without prejudice. This explains the inclusion in table 3 of cases in which the likelihood of securing beneficial results from conservative methods of treatment was extremely small. The number of failures was therefore somewhat larger than it would be under ordinary circumstances. It should be noted that absence of the posterior tibial pulse was a conspicuous feature in the cases in which poor results were obtained and that diabetes mellitus bore no relationship to the outcome of the treatment.

Thrombo-Angitis Obliterans—Table 4 epitomizes the data in a group of eight cases. Only two patients (25 per cent) obtained much relief.

TABLE 1—Data in Cases of *Arteriosclerosis Obliterans* (Good Results in 33 per Cent of Thirty-Nine Cases) *

Case No	Age	Sex	Reason for Treatment	Symptoms			Objective Manifestations						Pulses			Amount of Treatment, Hours	Results	Other Pathologic Conditions		
				Coldness	Paresthesias	Rest Pain	Claudication	Coldness	Permanent Changes in Color	Postural Changes in Color	Trophic Changes	Ulceration	Gangrene	Dorsalis Pedis	Posterior Tibial				Popliteal	Femoral
1	60	M	Refractory ulcer on right great toe	+	+	0	0	+	+	+	+	+	0	0	+	+	+	145	Ulcer healed rapidly	None
2	75	M	Refractory ulcer on right great toe	0	0	0	0	+	0	+	+	+	0	0	+	+	+	75	Ulcer healed, foot became warmer	Diabetes mellitus
3	69	M	Cold foot, pares thesias	+	+	0	0	+	+	0	+	0	0	+	+	+	+	10	Foot became warmer, paresthesia diminished	Diabetes mellitus, left leg previously amputated
4	58	F	Gangrene and chronic infection of right great toe	+	+	+	0	0	+	+	+	+	0	0	+	+	+	100	Toe sloughed, stump healed promptly	Diabetes mellitus
5	62	M	Intermittent claudication	+	+	0	+	+	0	0	+	0	0	0	+	+	+	50	Relieved of all distress	Pes planus
6	61	M	Refractory digital ulcer, cold foot	+	0	0	0	+	+	+	+	+	0	0	0	0	+	105	Ulcer healed promptly, foot became warmer	Diabetes mellitus, left leg previously amputated
7	68	M	Cold feet	+	+	0	0	+	0	0	0	0	+	+	+	+	+	10	Feet became warmer	None
8	67	M	Cold, painful feet, intermittent claudication	+	+	+	+	+	+	0	+	0	0	0	0	0	+	200	Feet became warmer, claudication disappeared	None
9	59	M	Stumps of two previously amputated toes would not heal	0	0	+	0	0	0	0	+	+	+	+	+	+	+	85	Healing greatly accelerated	Diabetes mellitus
10	61	M	Cold feet and intermittent claudication	+	+	0	+	+	0	0	+	0	0	0	0	0	+	150	Feet became warmer, patient could walk twice as far	Average blood pressure, 180 systolic and 130 diastolic
11	80	M	Painful, red feet	+	+	+	?	+	0	+	+	0	0	0	0	0	+	50	Pain relieved, color unchanged	Coronary arterio sclerosis, fatal pneumonia
12	78	M	Stump of previously amputated left great toe would not heal	+	+	+	0	+	+	0	+	+	0	0	+	+	+	20	Stump healed rapidly	Diabetes mellitus, right leg previously amputated
13	71	M	Painful, red feet	+	+	+	0	+	0	0	0	0	0	0	+	+	+	120	Pain relieved, color not appreciably changed	Average blood pressure, 200 systolic and 120 diastolic, varicose veins

* In this and the following tables a pulse is indicated as present (+) or absent (0), and in each case the top row represents the right side and the bottom the left side

TABLE 2—Data in Cases of Arteriosclerosis Obliterans (Fau Results in 25 per Cent of Thirty-Nine Cases)

Case	Age	Sex	Reason for Treatment	Symptoms			Objective Manifestations						Pulses			Amount of Treatment, Hours	Results	Other Pathologic Conditions
				Coldness	Paresthesias	Rest Pain	Claudication	Coldness	Permanent Changes in Color	Postural Changes in Color	Trophic Changes	Ulceration	Gangrene	Dorsalis Pedis	Posterior Tibial	Popliteal	Temporal	
1	66	M	Refractory ulcer on right great toe	+	+	+	+	+	+	0	+	+	0	0	0	++	++	Coronary arterio sclerosis
2	71	M	Painful, cold feet, claudication, refractory ulcer on toe	+	+	+	+	+	+	+	+	+	0	0	0	++	++	None
3	70	M	Painful refractory ulcer on right foot	+	+	+	0	+	0	0	+	+	0	+	+	+	+	Diabetes mellitus, left leg previously amputated
4	72	M	Painful ulcer on right heel	+	+	+	0	+	+	+	+	+	0	0	0	+	+	Diabetes mellitus, left leg previously amputated
5	42	F	Stump of previously amputated left great toe would not heal	0	0	+	0	0	0	0	0	+	+	+	+	+	+	Diabetes mellitus, right leg previously amputated
6	71	M	Cold, red, painful foot, refractory ulcer on toe	+	+	+	0	+	+	+	+	+	0	0	+	+	+	Pulmonary embolism, right leg previously amputated
7	60	M	Intermittent claudication	?	+	+	+	?	+	+	+	0	0	0	0	0	+	None
8	54	M	Stump of previously amputated toe would not heal	+	+	0	0	+	+	+	+	+	0	+	0	++	++	Diabetes mellitus
9	73	F	Stump of previously amputated toe would not heal	+	+	+	0	+	0	0	0	+	0	0	0	++	++	Diabetes mellitus
10	53	M	Intermittent claudication	+	+	0	+	+	+	+	?	0	0	0	+	+	+	None

Exercise tolerance doubled, feet became warmer

TABLE 3—Data in Cases of Arteriosclerosis

Case	Age	Sex	Reason for Treatment	Symptoms			Objective Manifestations						Pulses			Amount of Treatment, Hours	Results	Other Pathologic Conditions				
				Coldness	Paresthesias	Rest Pain	Claudication	Coldness	Permanent Changes	Changes in Color	Postural Changes	Trophic Changes	Ulceration	Gangrene	Dorsalis Pedis				Posterior Tibial	Popliteal	Femoral	
1	55	M	Gangrene and infection of one toe	+	+	+	+	+	+	0	+	+	+	0	0	0	0	0	0	207	Gangrene spread, requiring amputation of leg, stump treated unsuccessfully	Diabetes mellitus
2	75	M	Cold, painful feet, intermittent claudication	+	+	+	+	+	+	0	+	0	0	0	0	0	0	0	0	30	Began to improve, but cuffs caused so much discomfort that patient went home	Coronary arterio sclerosis
3	75	M	Painful, red left foot	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	45	Gangrene of two toes developed during treatment, necessitating amputation of leg	None
4	72	M	Painful, red right foot, with small ulcer	+	+	+	+	+	+	0	+	+	+	0	0	0	0	0	0	80	Ulcer enlarged, gangrene developed	Coronary arterio sclerosis
5	66	M	Large refractory ulcer on left heel	+	+	+	0	+	+	0	+	+	+	0	0	0	0	0	0	35	Ulcer enlarged and became more painful	Diabetes mellitus
6	75	M	Claudication	+	0	0	+	+	+	0	+	0	0	0	0	0	0	0	0	22	No improvement, treatment discontinued because cuffs blistered thighs	Coronary arterio sclerosis
7	72	M	Severe intermittent claudication	+	+	0	+	+	+	+	+	+	0	0	0	0	0	0	0	80	No improvement	Coronary arterio sclerosis
8	52	M	Cold feet, intermittent claudication	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	15	Treatment produced pain in feet, cuffs caused discomfort	Latent syphilis
9	74	M	Gangrene of dorsum of left foot	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	60	Gangrene spread, necessitating amputation	None
10	68	M	Stump of previously amputated toe would not heal	+	+	+	0	+	+	0	+	0	0	0	0	0	0	0	0	80	Healing slightly accelerated, pain unrelieved	Diabetes mellitus
11	65	M	Stump of previously amputated right leg would not heal	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	35	No improvement	Average blood pressure, 200 systolic and 108 diastolic, left leg previously amputated
12	62	M	Red, painful right foot, with two small ulcers	?	+	+	+	+	+	0	+	+	+	0	0	0	0	0	0	95	No relief from pain, ulcers became larger	None
13	55	F	Stump of previously amputated toe would not heal	+	+	+	0	+	+	0	+	+	+	0	0	0	0	0	0	35	Treatment caused pain, healing not accelerated	Diabetes mellitus, right leg previously amputated
14	68	F	Left foot cold and painful, dry gangrene of one toe	+	+	+	0	+	+	0	+	+	+	0	0	0	0	0	0	90	Foot became warmer, but an ulcer appeared on heel, amputation will be necessary	Average blood pressure, 250 systolic and 110 diastolic, uremia, diabetes, right leg previously amputated
15	58	M	Gangrenous, painful toe	+	+	+	0	+	+	0	+	+	+	0	0	0	0	0	0	20	Treatment increased pain and was discontinued, toe amputated successfully	Left leg previously amputated
16	68	F	Cold, red, painful feet, with ulcers on two toes	+	+	+	0	+	+	+	+	+	+	0	0	0	0	0	0	35	Treatment increased pain, feet remained cold, ulcers unaffected	Diabetes mellitus

TABLE 4—Data in Cases of *Thrombo-angiitis Obliterans*

Case	Age	Sex	Reason for Treatment	Symptoms			Objective Manifestations						Pulses					Amount of Treatment, Hours	Results	Other Pathologic Conditions					
				Coldness	Paresthesias	Rest Pain	Claudication	Coldness	Permanent Changes in Color	Postural Changes in Color	Phlebitis	Trophic Changes	Ulceration or Gangrene	Radial	Ulnar	Dorsalis Pedis	Posterior Tibial				Popliteal	Femoral			
1	55	M	Rest pain, intermittent claudication	0	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	195	Good rest pain and claudication greatly relieved	None
2	41	M	Ulcer on index finger of left hand, rest pain in hand	+	+	+	0	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	128	Good, pain relieved, ulcer healed rapidly	None
3	35	M	Small ulcer on left foot, rest pain	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	135	Fair, pain somewhat relieved, ulcer unaffected	None
4	39	M	Intermittent claudication	0	0	+	+	+	+	0	+	0	0	0	0	0	0	0	0	0	0	0	100	Poor, no relief from claudication	History of coronary occlusion
5	47	M	Painful, red feet, intermittent claudication	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	185	Poor, no improvement	None
6	56	M	Painful, red feet, stump of previously amputated toe not healing	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	300	Poor, some relief from pain, ulcer grew smaller but enlarged again later	None
7	43	M	Painful, red feet, ulcers on two toes of left foot	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	117	Poor, pain unrelieved, ulcers enlarged	None
8	39	M	Intermittent claudication	+	+	+	+	+	+	+	0	+	+	+	0	0	0	0	0	0	0	0	100	Poor, no improvement	None

TABLE 5—Data in Cases of Sudden Iliac Occlusion

Case	Age	Sex	Reason for Treatment	Symptoms			Objective Manifestations										Pulses					Amount of Treatment, Hours	Results	Other Pathologic Conditions
				Coldness	Paresthesias	Rest Pain	Claudication	Coldness	Permanent Changes in Color	Postural Changes in Color	Trophic Changes	Ulceration	Gangrene	Radial	Ulnar	Dorsalis Pedis	Posterior Tibial	Popliteal	Iliac					
1	34	F	Occlusion of right popliteal artery 3 mo earlier, gangrenous ulcer occupying one half of sole of foot	+	+	+	0	+	+	0	+	+	+	+	+	+	+	+	+	+	+	87	Good, ulcer healed rapidly, foot became warm and painless, no return of pulses	Severe rheumatic heart disease, auricular fibrillation
2	60	F	Occlusion of abdominal aorta at bifurcation 8 mo earlier, severe bilateral claudication	0	0	0	+	+	0	0	0	0	0	0	0	+	+	0	0	0	0	122	Good, claudication greatly relieved	Average blood pressure, 210 systolic and 95 diastolic, generalized arteriosclerosis
3	45	F	Occlusion of right brachial artery a few hours earlier, cold, painful hand	+	+	+	0	+	+	0	0	0	0	0	0	+	+	+	+	+	+	12	Good, hand became warm, pain relieved, small radial pulse appeared	Mild rheumatic heart disease, auricular fibrillation
4	54	M	Occlusion of left popliteal artery 5 mo earlier, severe claudication and rest pain	+	+	+	+	+	+	+	+	0	0	0	0	+	+	0	0	0	+	346	Good, after 136 hrs of treatment pain nearly abolished, after 210 hrs, 4 mo later, pain abolished completely, foot remained somewhat cool	Coronary arterio sclerosis, auricular fibrillation, thromboangitis obliterans (?)
5	60	M	Occlusion of left popliteal artery an hour earlier, cold, painful foot	+	+	+	0	+	+	0	0	0	0	0	0	+	+	0	0	0	+	32	Good, foot became warmer than its fellow, pain and numbness disappeared	Average blood pressure, 130 systolic and 110 diastolic, history of coronary occlusion of coronary arterio sclerosis
6	86	M	Occlusion of right popliteal artery 24 hrs earlier, red, painful foot	+	+	+	0	+	+	+	0	0	0	0	0	—	—	0	0	+	+	45	Good, foot became warmer and practically painless, patient died of pneumonia	Coronary arterio sclerosis
7	18	M	Ligation of right femoral artery just below first perforating branch 1 yr earlier, claudication, cold foot	+	+	0	+	?	0	0	0	0	0	0	—	—	+	+	0	0	+	100	Good, could walk twice as far, pares thesias disappeared, foot warmer	None
8	47	M	Occlusion of arteries of three fingers of right hand 1 mo earlier, cold, numb fingers	+	+	0	0	+	+	0	0	0	0	0	+	+	0	+	+	+	+	100	Good, fingers became much warmer, pares thesias practically disappeared	None
9	65	M	Occlusion of right brachial artery 3 weeks earlier, cold, numb hand	+	+	0	0	+	+	0	0	0	0	0	+	+	0	+	+	+	+	18	Fair, hand became warmer, but patient refused further treatment	None
10	76	F	Occlusion of right popliteal artery 5 days earlier, cold, painful foot	+	+	+	0	+	+	0	0	0	0	0	—	—	0	+	+	0	+	24	Fair, foot warmer, pain not entirely relieved	Coronary arterio sclerosis, old hemiplegia
11	54	M	Occlusion of left popliteal artery 1 mo earlier, cold, discolored painful foot	+	+	+	0	+	+	+	0	0	0	0	—	—	+	0	+	0	+	25	Poor, leg became warmer, but discoloration deepened, amputation necessary	Mild rheumatic heart disease, auricular fibrillation
12	65	F	Occlusion of left brachial artery an hour earlier, cold, painful hand	+	+	+	0	+	+	0	0	0	0	0	+	+	—	—	—	—	—	7	Poor, no relief of pain or change of color, but patient died in circulatory collapse 12 hours later	Coronary arterio sclerosis, mesenteric thrombosis

TABLE 6—Data in Cases of Miscellaneous Disorders

Case	Age	Sex	Reason for Treatment	Symptoms			Objective Manifestations										Pulses			Amount of Treatment, Hours	Results	Other Pathologic Conditions
				Coldness	Paresthesias	Rest Pain	Coldness	Permanent Changes in Color	Postural Changes in Color	Trophic Changes	Ulceration	Gangrene	Radial	Ulnar	Dorsalis Pedis	Posterior Tibial	Popliteal	Femoral				
1	72	M	Foot frozen several weeks earlier, stumps of several toes which had sloughed were healing poorly	0	+	+	0	+	0	0	0	+	0	0	++	++	++	++	30	Healing somewhat accelerated	None	
2	34	M	Hand exposed to severe cold a few hours earlier, severe pain	0	+	+	0	+	0	0	0	0	0	0	++	++	++	++	4	Pain relieved completely	None	
3	57	F	Raynaud's disease, arteriosclerosis obliterans, small ulcer on one toe	+	+	+	+	+	0	+	+	+	0	0	++	++	++	++	5	No improvement, pain aggravated by treatment	Coronary arterio sclerosis, average blood pressure, 180 systolic and 100 diastolic	
4	39	M	Raynaud's disease, ulcer on tip of right index finger	+	+	+	+	+	0	0	+	+	0	0	++	++	++	++	42	Pain somewhat relieved only during actual treatment, healing of ulcer accelerated	Peptic ulcer of duodenum	
5	25	M	Arterial insufficiency after local anesthesia of right index finger 1 week earlier, small ulcer on finger tip	+	+	+	+	+	0	0	0	+	0	0	++	++	++	++	26	Pain relieved, finger became warmer, ulcer healed slowly	None	
6	16	M	Refractory ulcers of uncertain origin on both legs (varicose)	0	0	0	0	0	0	0	0	+	0	0	++	++	++	++	90	No improvement	Chronic glomerular nephritis	
7	54	M	Refractory ulcers on both feet, probably due to disease of spinal cord	0	0	0	0	+	+	+	+	+	0	0	—	—	++	++	55	No improvement	Congenital malformation of spinal cord (?)	
8	26	M	Obscure vasomotor disturbance	0	+	+	+	+	0	0	0	0	0	0	++	++	++	++	120	No improvement	Generalized arterio sclerosis and capillary fibrosis, chronic diffuse nephritis (necropsy)	
9	28	M	Three toes of left foot frozen several months earlier, severe rest pain, small ulcer on great toe	+	+	+	+	+	+	+	+	+	0	0	++	++	++	++	5	No improvement, pain aggravated by treatment, foot amputated	Histologic appearance not that of thrombo angitis obliterans	

Sudden Occlusion of a Major Artery—Although this is not a progressive obliterative process and a patient may recover unaided even from occlusion of the abdominal aorta at its bifurcation, it is nevertheless obvious that passive vascular exercise increases enormously the likelihood and rapidity of restitution in integrum. This noteworthy achievement is in itself sufficient recompense for all the time and effort which have been expended in developing the method. Table 5 summarizes our experience in twelve cases. In spite of the fact that in most of these cases treatment was not started until long after the occlusion had occurred, the results were excellent in all but the last two cases, and in those cases the condition was virtually hopeless from the beginning. Case 1 deserves particular notice. Three months after sudden occlusion of the right popliteal artery, all the characteristic manifestations of arterial insufficiency, including gangrenous ulceration of half the sole of the foot, were present. After eighty-seven hours of treatment were given, recovery was practically complete.

Miscellaneous Conditions—Reference to table 6 shows that passive vascular exercise is not a panacea and should not be employed indiscriminately. In this group only the immediate consequences of frostbite (case 2) and arterial insufficiency secondary to local anesthesia (case 5) proved amenable to treatment by this method.

SUMMARY

This report is, in its entirety, a summary. Our experience indicates, as does that of many other observers, that if collateral pathways are potentially adequate, passive vascular exercise helps to reestablish the circulation in an extremity which has been deprived of part of its blood supply by obliterative arterial disease.

EFFECT OF MAGNESIUM ON VASCULAR SPASM IN RATS

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AND

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PHILADELPHIA

In a previous study it was demonstrated that the magnesium ion is capable of preventing the contraction of smooth muscle both in vitro and in vivo¹. In a large percentage of guinea-pigs passively sensitized to horse serum an intravenous injection of magnesium chloride just prior to the injection of a shocking dose of horse serum prevented the appearance of anaphylactic shock. Similarly, the addition of magnesium chloride in isotonic amounts to the fluid of the Dale bath in which were suspended uterine strips from sensitized guinea-pigs prevented the contraction of the strips when antigen was added.

EXPERIMENTS

The present studies were concerned with the effect of the magnesium ion on the contraction of the smooth muscle of the vascular system in the intact animal. White rats (Wistar strain) were utilized as the experimental animals, and the systolic blood pressure was used as an index of the presence or absence of vascular spasm. The technic employed for the determination of the systolic blood pressure in the rat was the indirect method of Griffith².

Technic of Measuring the Systolic Blood Pressure—The apparatus employed in determining the rat's blood pressure is illustrated in figure 1. The rat is kept under constant and complete ether anesthesia during the period of determination, for it has been found that with the animal under light anesthesia his movements produce fluctuations in the blood pressure. The dorsum of the hindleg is shaved, care being taken to avoid traumatizing the skin, as this produces multiple thromboses of small vessels and interferes with the determination of the blood pressure.

The blood pressure cuff is made from a ring of thin elastic sheet rubber with an internal diameter of about $\frac{1}{2}$ inch (1.3 cm) and a width of about $\frac{3}{8}$ inch (1 cm). The cuff is reinforced on the outer side with several thicknesses of

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1 Rubin, M I. Studies on Anaphylaxis (unpublished), presented before the Pediatric Research Society, Atlantic City, N J, May 3, 1932.

2 Griffith, J Q, Jr. Indirect Method for Determining Blood Pressure in Small Animals, Proc Soc Exper Biol & Med **32** 394, 1934.

sheet rubber to prevent bulging. The cuff is connected to one arm of a Y tube. The second arm of the Y tube is connected to a standard mercury manometer and the third arm to a rubber compression bulb. The rubber bulb is kept in a wooden box, where constant pressure may be applied with a screw clamp.

The leg of the rat, after the cuff is applied to the thigh, is supported on the microscopic stage with plasticine. The small cutaneous vessels on the dorsum of the shaved leg are observed under liquid petrolatum with the low power objective of the microscope, indirect illumination being used. Cutaneous vessels in which the flow of blood is very rapid are chosen for observation. The movement of the column of blood in suitable vessels is continuous and so rapid that individual blood cells cannot be distinguished.

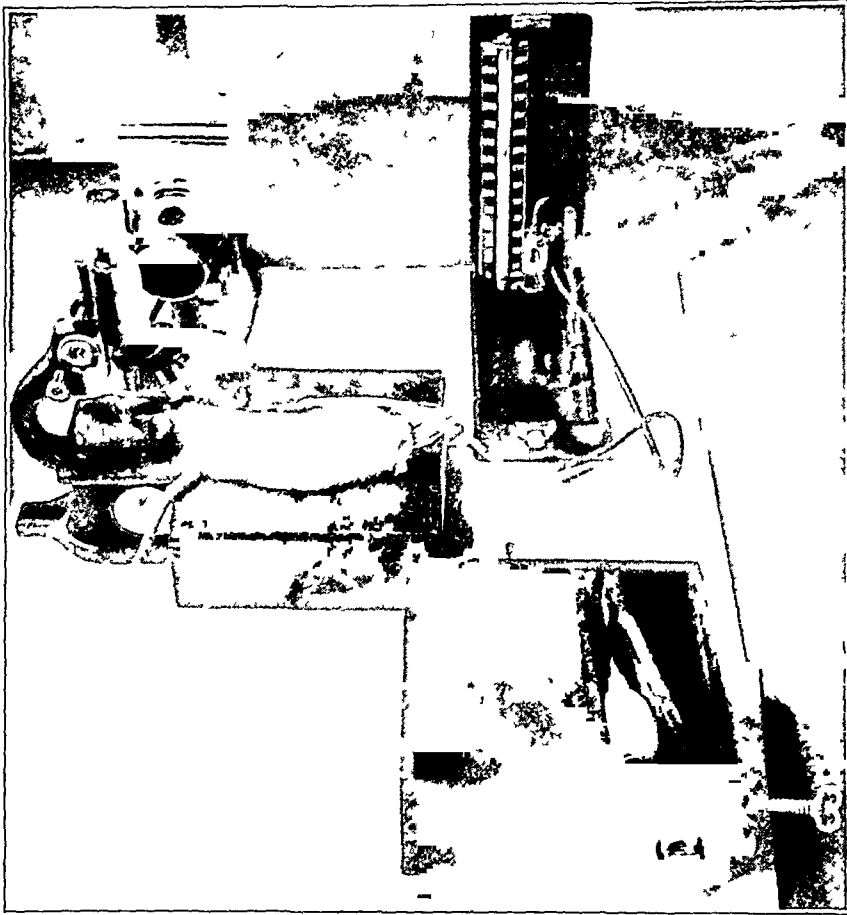


Fig 1—The apparatus employed in determining the systolic blood pressure of the rats

Pressure is applied to the rubber bulb in increments of from 2 to 4 mm of mercury while the vessels are kept under constant observation. The pressure necessary to stop the flow of blood in the small vessels is taken as the systolic blood pressure of the animal. The average of three consecutive readings is considered the final reading, provided the individual readings do not vary more than 15 mm of mercury. After many readings have been taken, edema of the leg often develops and renders it unsuitable for further observation at the time. If further readings are required, the other hindleg is used.

Griffith² has shown that the readings of the systolic blood pressure of rats taken by this indirect method are comparable with the direct readings obtained

by inserting a needle into a large artery. The values obtained by us for the systolic blood pressure of normal rats are similar to those found by Griffith³ and co-workers and by Leiter,⁴ who also measured the blood pressure by cannulization of the arteries.

Experimental Data—Persistent vascular spasm with resultant hypertension was produced by the parenteral administration of ergotamine tartrate⁵. There is adequate evidence to show that this drug produces intense vasoconstriction. Herrick⁶ found that from 0.5 to 1 mg of this drug given parenterally markedly reduced the blood flow in the femoral artery of the dog and raised the systemic blood pressure. Pool and Nason⁷ by direct observation with the microscope demonstrated constriction of the dural and the cutaneous arteries after the administration of ergotamine. Lewis⁸ has shown that there is intense, per-

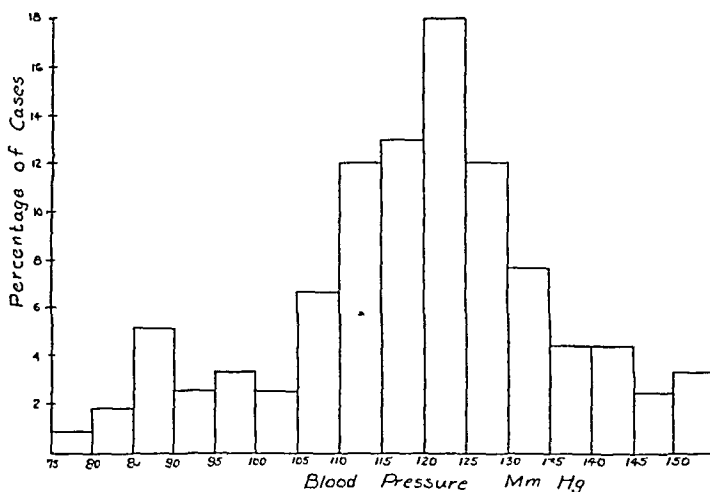


Fig 2—The distribution of blood pressure readings for one hundred and seventeen normal rats

3 Griffith, J Q, Jr, Jeffers, W A, and Lindauer, M A. A Study of the Mechanism of Hypertension Following Intracisternal Kaolin Injection in Rats. Leucocytic Reaction and Effect on Lymphatic Absorption, *Am J Physiol* **113** 284, 1935

4 Leiter, L. The Nonspecific Role of Pressor Substances in the Plasma of Hypertensive Patients, *Arch Int Med* **57** 729 (April) 1936

5 The ergotamine tartrate used in these experiments was supplied by the Sandoz Chemical Works, Inc

6 Herrick, J F. Effect of Ergotamine Tartrate on Blood Flow and Blood Pressure in the Femoral Artery of the Dog, *Proc Soc Exper Biol & Med* **30** 271, 1933

7 Pool, J L, and Nason, G I. Cerebral Circulation. The Comparative Effect of Ergotamine Tartrate on the Arteries in the Pia, Dura and Skin of Cats, *Arch Neurol & Psychiat* **33** 276 (Feb) 1935

8 Lewis, T, and Gelfand, B. The Manner in Which Necrosis Arises in the Fowl's Comb Under Ergot Poisoning, *Clin Sc* **2** 43, 1935

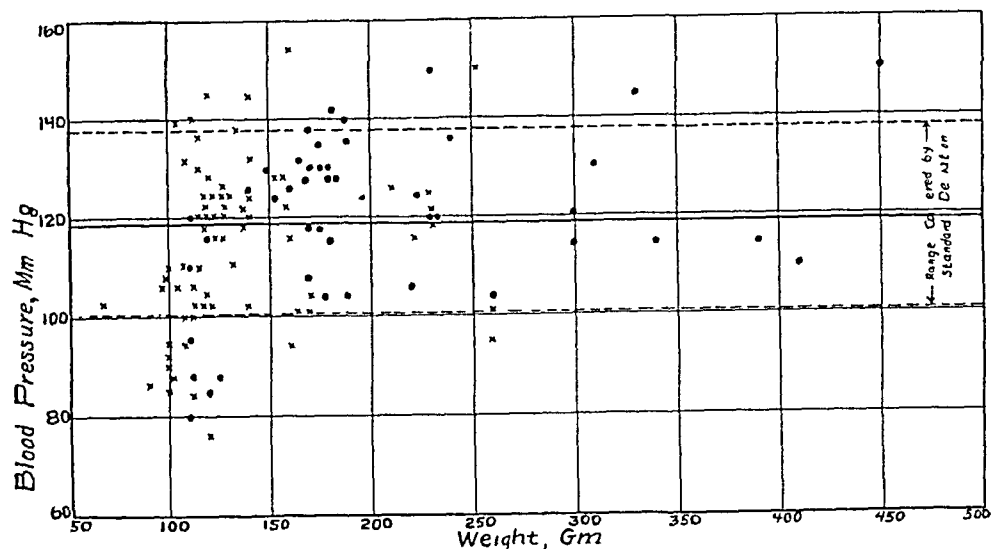


Fig 3—The normal blood pressure levels for rats of both sexes and different weights. The black circles indicate males and the crosses females.

Data on the Systolic Blood Pressure of Rats

Systolic Blood Pressure, mm Hg	Normal Rats			Rats Given Ergotamine Tartrate					
	Number of Rats	Normal Diet		Normal Diet			Magnesium Diet		
		Cumu lative Number of Rats	Cumu lative Percent age of Rats	Number of Rats	Cumu lative Number of Rats	Cumu lative Percent age of Rats	Number of Rats	Cumu lative Number of Rats	Cumu lative Percent age of Rats
75-79	1	1	0.86						
80-84	2	3	2.55						
85-89	6	9	7.70						
90-94	3	12	10.20				1	1	1.5
95-99	4	16	13.70						
100-104	3	19	16.30				8	9	13.8
105-109	8	27	23.00				7	16	25.4
110-114	14	41	35.80				4	20	30.8
115-119	15	56	47.80				7	27	42.8
120-124	16	72	61.70				13	40	61.5
125-129	14	86	73.80				6	46	73.0
130-134	9	95	80.50	2	2	3.2	6	52	82.5
135-139	5	100	85.50				3	55	87.3
140-144	5	105	89.90	1	3	4.8	5	60	92.3
145-149	3	108	92.50				1	61	94.0
150-154	4	112	96.00	1	4	6.4			
155-159				1	5	7.8			
160-164				7	12	19.1	1	62	95.5
165-169				4	16	25.4			
170-174				7	23	36.5	1	63	97.0
175-179				9	32	50.9	2	65	100.0
180-184				3	35	55.5			
185-189				2	37	58.6			
190-194				6	43	68.3			
195-199				2	45	71.5			
200-204				7	52	82.5			
205-209				1	53	84.2			
210-214				2	55	87.5			
215-219				5	60	95.2			
220-224				1	61	96.8			
225-229				1	62	97.8			
230-234				2	63	100.0			
Average systolic blood pressure 119 mm Hg \pm 19 (S.D.)				Average systolic blood pressure 185 mm Hg \pm 23 (S.D.)			Average systolic blood pressure 121 mm Hg \pm 18 (S.D.)		

sistent vasoconstriction in the comb of the fowl treated with ergotoxine, the duration of the vascular spasm varying with the dose of the drug

Blood Pressure of Normal Rats—The accompanying table and figures 2 and 3 show the variations in the systolic blood pressure of one hundred and seventeen normal rats raised on our colony diet

Composition of Diet	Gm
Whole ground wheat	660
Whole ground corn	680
Whole milk powder	420
Linseed oil meal	140
Alfalfa meal	40
Liver	40
Calcium carbonate	10
Sodium chloride	10
Dried brewer's yeast	40

It is apparent that weight and sex do not influence the blood pressure significantly. The range of these normal blood pressures was from 78 to 154 mm of mercury, the average being 119, with a standard deviation of ± 19 . It is interesting that 69 per cent of the values obtained by Leiter, who used the direct method, fell between 101 and 140 mm of mercury and that the range of blood pressures covered by our standard deviation, which included 68.26 per cent of the total readings, was between 100 and 138 mm of mercury. Repeated readings for the same rat showed no significant fluctuations.

Blood Pressure of Rats Given Injections of Ergotamine Tartrate—One hundred and twenty-eight rats, weighing from 75 to 100 Gm at the onset of the experiment, were divided into two equal groups on the basis of weight and sex. One group was kept on the diet for the normal colony, the other group was given the same diet, to which 2 per cent of magnesium carbonate by weight was added. Magnesium carbonate when fed at this level did not produce diarrhea in the rats. The stools, however, were soft and pasty. After the rats had been on these diets for about three weeks the blood pressure was determined, and then the animals in both groups were given subcutaneous injections of 15 mg of ergotamine tartrate per kilogram of body weight. Some animals in each group received but one injection, others received two injections and still others received three injections at weekly intervals. In no case was the subsequent blood pressure reading recorded prior to one week after the last injection. In some cases the readings were not taken until from two to five weeks after the last injection. In every instance, however, the readings were paired, the animals on different diets being studied at the same time.

The accompanying table and figure 4 show the blood pressure levels of the rats on the two diets which were given ergotamine. Ninety-four per cent (or sixty-one) of the sixty-five animals on the magnesium diet had a systolic blood pressure which was well within the normal range. Ninety-three and six-tenths per cent (or fifty-nine) of the sixty-three animals on the normal diet, however, had hypertension.

In one experiment (figs 5 and 6) after the effect of ergotamine on two groups of rats had been determined the diets were reversed. The group of animals in which hypertension had developed when they were given the normal diet responded with a fall in blood pressure to within normal range when placed on

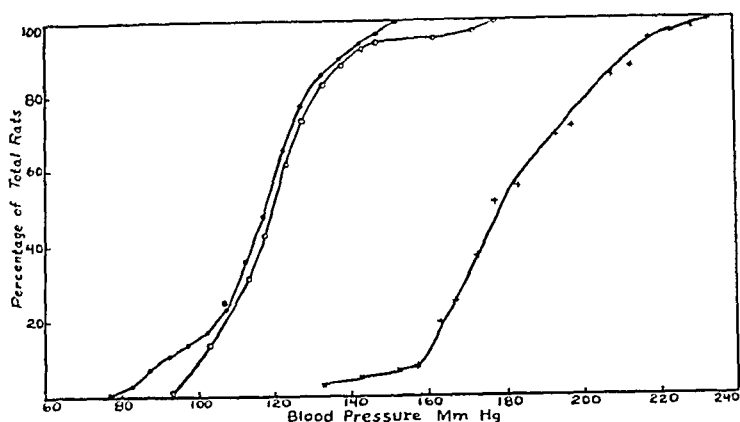


Fig 4—Cumulative frequency curves of the blood pressure readings for three groups of rats. The black circles indicate the readings for one hundred and seventeen normal rats which were fed a normal diet, the white circles indicate the readings for sixty-five rats which were fed a magnesium-containing diet and given injections of ergotamine tartrate, and the crosses indicate the readings for sixty-three rats fed a normal diet which were given injections of ergotamine tartrate.

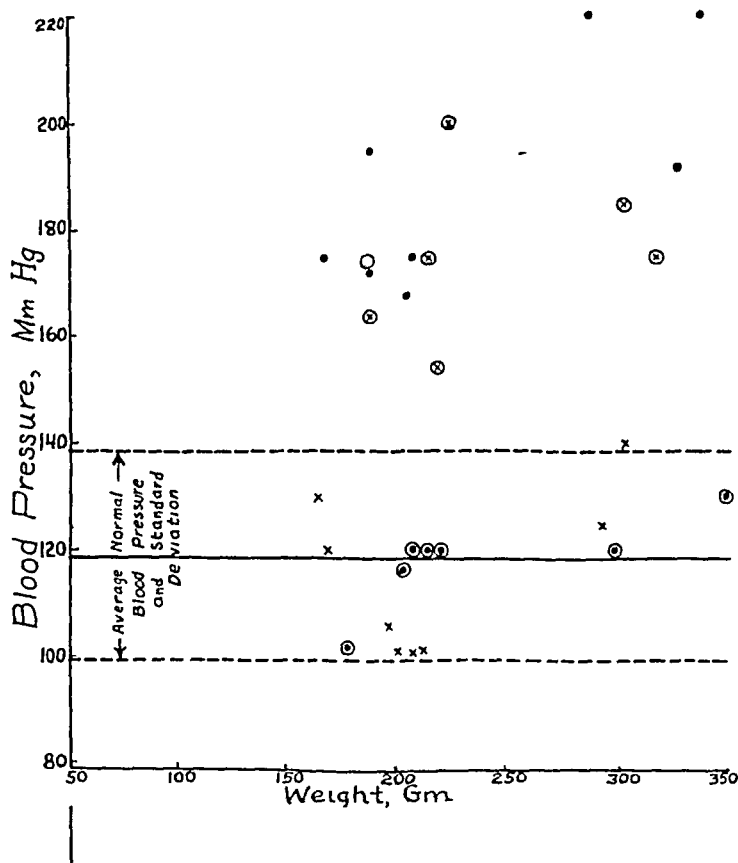


Fig 5—The blood pressure readings for rats which were given injections of ergotamine tartrate and which were maintained on different diets, the effect of reversing the diets being noted. The solid black circles represent readings for rats on a normal diet, the white circles with a solid black center, the readings for rats changed from a normal to a magnesium-containing diet, the crosses, the readings for rats fed on a magnesium-containing diet, and the white circles with a cross in the center, the readings for rats changed from a magnesium-containing to a normal diet.

the magnesium diet Conversely, the animals which had failed to show hypertension while on the magnesium diet responded with a rise in blood pressure when magnesium was withdrawn from the diet These changes in blood pressure were produced forty days after the injections of ergotamine tartrate were given Readings were taken for another thirty days, and the effects were still operative The implication of this experiment, in which the reversal in the blood pressure readings could be effected as long as forty days after the injection of three doses of ergotamine tartrate, is that the effect of magnesium is not to rid the body of the ergotamine but to hold in abeyance the vasoconstricting action of the drug

Effect of Ergotamine on Growth and Development—The weight curves for both groups of rats which had been given ergotamine, i e, those on the normal diet and those on the magnesium diet, were below the average weight for our

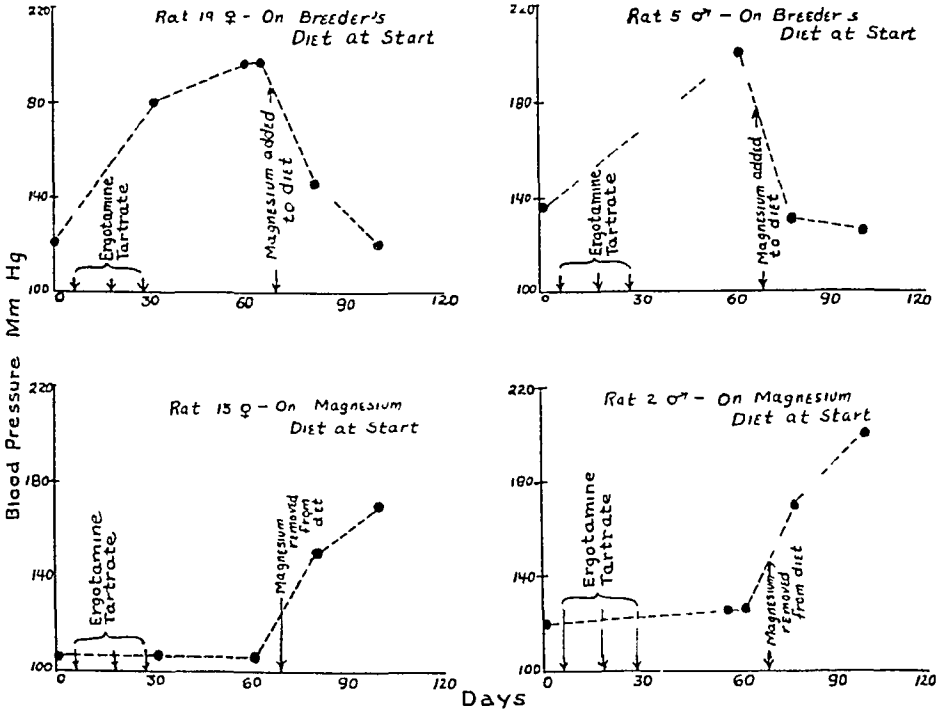


Fig 6—Graphs showing the effect of adding magnesium to and removing magnesium from the diet

normal colony rats A comparison of weight curves showed no difference between the animals on the normal diet and the animals on the magnesium diet sixty days after the last injection of ergotamine tartrate

Because diets high in magnesium have been used to produce rickets in the rat,⁹ roentgenographic studies were carried out on our animals to determine whether or not osseous changes had occurred No detectable differences in the density or the structure of the bones were evident in the roentgenograms of the rats fed the normal diet and rats fed the magnesium diet

Pathologic Observations—Peripheral gangrene of the tail developed in almost all the animals on both diets which were given ergotamine This lesion was

9 Meyer zu Horste, G Magnesium Rachitis, Monatschr f Kinderh 54 195, 1932, Klin Wchnschr 11 1796, 1932

similar to that described by McGrath¹⁰ in the rats tail and by Lewis and Gelfand⁸ in the fowl's comb. The tails of the rats in this experiment were studied by Dr Arthur D. Waltz, pathologist for the Children's Hospital, and the following report was made:

"Sections of the gangrenous tails show the epidermis shrunken and the areolar connective tissue pale, containing small clear fluid spaces. The muscle fibers are granular, the striations lost and the muscles degenerated. Practically all the arterioles contain thrombi in different stages of formation, those of more recent origin consist largely of fibrin containing sinuses filled with erythrocytes. These vessel walls show areas of the intima denuded of lining endothelium, the appearance of the rest of the wall is normal. Other thrombi are well organized and partially canalized. Occasionally a vessel and its contained thrombus are definitely degenerated. All other blood vessels, from the smallest capillaries to the comparatively large vessels, are greatly dilated and packed with red blood cells. There are no noteworthy changes in the bone."

The urine of both groups of rats which were given ergotamine contained albumin. No organized sediment was present.

COMMENT

There is ample evidence that ergotamine tartrate produces vasoconstriction in the intact animal. Since the early description of the action of ergot by Dale,¹¹ in which he stated that one of the major effects of this drug is direct stimulation of the smooth musculature of arteries producing contraction, many other workers have confirmed this observation.¹² This vascular spasm, we believe, is directly responsible for the hypertension produced in our rats. A rise in the systolic blood pressure following the administration of ergotamine tartrate has been observed by Herrick⁶ in the dog, by Pool and Nason⁷ in the cat and by Pool, von Storch and Lennox¹³ in human beings. While the rises in the systolic blood pressure reported by these workers were not of as great magnitude as those reported in this paper, it should be emphasized that the doses of ergotamine which they employed were much smaller than those utilized in our experiment.

Studies by the general physiologist show that the magnesium ion is capable of producing relaxation of the smooth muscle fiber. Thus Tren-

10 McGrath, E. J. G. Experimental Peripheral Gangrene. Effect of Estrogenic Substance and Its Relation to Thrombo-Angitis Obliterans, *Arch. Int. Med.* **55** 942 (June) 1935.

11 Dale, H. H. On Some Physiological Actions of Ergot, *J. Physiol.* **34** 163, 1906.

12 Herrick⁶, Pool and Nason⁷, Lewis and Gelfand⁸, Heymans, C., Bouckaert, J. J., and Moraes, A. Au sujet de l'action vasculaire de l'ergotamine: inversion de l'action vaso-constrictrice des "vasotonines" du sang defibriné par l'ergotamine, *Compt. rend. Soc. de biol.* **110** 993, 1932.

13 Pool, J. L., von Storch, T. J. C., and Lennox, W. G. Effect of Ergotamine Tartrate on Pressure of Cerebrospinal Fluid and Blood During Migraine Headache, *Arch. Int. Med.* **57** 32 (Jan.) 1936.

delenburg¹⁴ was able to produce relaxation of the smooth muscle of the bronchi, and Wiechmann¹⁵ demonstrated a similar effect on the smooth musculature of isolated strips of stomach and intestine. Teschen-dorf,¹⁶ using strips of the musculature of the skin of the leech, which is a pure smooth muscle, was also able to relax the intense spasm induced by barium chloride and prevent contraction from faradic stimulation by adding magnesium chloride to the bathing fluid. As has been mentioned previously, we have been able to prevent spasm of the smooth muscle of the passively sensitized guinea-pig both in vivo and in vitro with the magnesium ion.¹ These studies on preparations of isolated smooth muscle furnish strong evidence that magnesium acts directly on the smooth muscle fiber. However, Wiechmann pointed out that he was able to demonstrate a paralyzing action on the myoneural junction in addition to the direct paralyzing action on the muscle fiber.

From this evidence it is our belief that magnesium relieved the hypertension in the rats which were given ergotamine by a peripheral relaxing action on the smooth muscle coats of the blood vessels. There was no evidence that the narcotic action of magnesium played any rôle in effecting this reduction in blood pressure. The rats fed on the magnesium diet were always active. Demonstrable dehydration was not produced in the animals on the magnesium diet and therefore cannot be considered as the mechanism for reducing the blood pressure.

As has been pointed out, in rats on both diets which were given ergotamine gangrene of the tail developed. It is felt that the failure of the magnesium ion to prevent this change in the tail was due to the fact that the vasoconstriction immediately following the injection of the large doses of ergotamine tartrate is so intense that the relaxing effect of magnesium when given by mouth is inadequate. This is further substantiated by our observation that the blood pressure is elevated in both groups of animals immediately after the injection of ergotamine and that the observed differences in pressure are apparent only after about one week. It is possible, however, that magnesium administered parenterally might be effectual in preventing the intense vascular spasm which is primarily responsible for the gangrene.

In one group of rats, not included here, in which the blood pressure was maintained within normal limits with the magnesium diet after three

14 Trendelenburg, P. Physiologische und pharmakologische Untersuchungen an der isolierten Bronchialmuskulatur, *Arch f exper Path u Pharmakol* **69** 79, 1912.

15 Wiechmann, E. Zur Theorie der Magnesium Narkose, *Arch f d ges Physiol* **182** 74, 1920.

16 Teschen-dorf, W. Beitrage zur Physiologie und Pharmakologie der Blutegebmuskulatur, *Arch f d ges Physiol* **192** 135, 1921.

injections of ergotamine, after the injection of three additional doses of ergotamine tartrate the blood pressure was no longer controlled by the magnesium diet in some of the animals

The clinical implications of this study are obvious. They suggest that the beneficial action of magnesium in lowering the hypertension in the acute phase of hemorrhagic nephritis may in a large measure be due to its relaxing effect on the musculature of the spastic vessels responsible for the elevation of the blood pressure. They further suggest that magnesium may be of therapeutic value in various vascular spastic states with or without hypertension.

SUMMARY

Hypertension was produced in rats by the parenteral injection of ergotamine tartrate.

Magnesium carbonate when added to the diet reduced the blood pressure of rats that had been rendered hypertensive to within normal limits.

The action of the magnesium ion in relieving this experimental hypertension is believed to be due to its relaxing effect on the smooth musculature of the blood vessels.

The clinical implications of this study are suggested.

Progress in Internal Medicine

LIVER AND BILIARY TRACT

A REVIEW FOR 1936

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NEW YORK

The clinical literature dealing with diseases of the liver and the biliary tract continues to be voluminous. Much of it deals with case reports and clinical discussions, hence detailed summary is not necessary. We have sought, therefore, not to attempt a comprehensive review of this literature but to follow the plan used in previous reviews of this series¹ and to limit our discussion to selected subjects in which there have been noteworthy contributions. Even in these subjects we make reference to selected articles rather than give an inclusive bibliography.

PHYSIOLOGY OF THE BILIARY TRACT

Pressure Relationships Within the Biliary Tract—It is generally accepted that the secretion of bile by the liver is continuous, but its discharge into the duodenum is intermittent. Both the discharge of bile into the duodenum and the filling and emptying of the gallbladder are controlled by the choledochal-duodenal sphincter—the sphincter of Oddi. Numerous observers have studied the pressure relationships within the biliary tract since the initial experiments of Doyon² and of Bainbridge and Dale³. These studies have been summarized by Ivy⁴.

From the Clinic for Diseases of the Liver and Biliary Tract of the Departments of Medicine and Surgery, the New York Post-Graduate Medical School and Hospital and the Long Island College Division of the Kings County Hospital.

1 Greene, C H, Bercovitz, Z and Hanssen E C. Liver and Biliary Tract. Review of the Literature for 1933 and 1934, Arch Int Med **55** 681-706, (April) 1935.

2 Doyon, M. Mouvements spontanés des voies biliaires, Arch de physiol norm et path **5** 710-719, 1893.

3 Bainbridge, F A, and Dale, H H. The Contractile Mechanism of the Gall-Bladder and Its Extrinsic Nervous Control, J Physiol **33** 138-155, 1905-1906.

4 Ivy, A C. The Physiology of the Gall Bladder, Physiol Rev **14** 1-102, 1934.

Most of the experiments were performed on anesthetized animals, but Higgins and Mann,⁵ Potter and Mann,⁶ McMaster and Elman,⁷ and Ivy and Oldberg⁸ so arranged their experiments that they were able to obtain readings on unanesthetized dogs

They found that the sphincter of Oddi in the resting animal possesses a definite tonus and is able to withstand a pressure of from 90 to 250 mm of water. This is greater than the pressure, 100 mm, in the resting gallbladder, so that in the fasting animal the secreted bile is stored in the gallbladder. After a meal the sphincter relaxes and the gallbladder contracts and empties. The maximal pressure developed in the gallbladder during contraction varies from 210 to 270 mm of bile.

The maximal pressure under which bile is secreted by the liver, according to the reports of Naunyn,⁹ Herring and Simpson,¹⁰ Mitchell and Stifel,¹¹ Mann and Foster,¹² McMaster and Elman⁷ and others, varies, in the dog, from 240 to 310 mm of water. This pressure under ordinary circumstances is greater than the contractile force of either the gallbladder or the sphincter of Oddi, so that the liver normally is protected against the effects of back pressure. However, Ivy reported that spasm of the sphincter may occasionally produce a pressure of 800 mm of water. Spasm of such intensity not only would prevent evacuation of the gallbladder but would cause biliary colic and if it persisted, jaundice.

Less is known regarding the pressure relationships in the human biliary tract, though presumably they are similar to those in the dog. Robitschek and Turlot¹³ in 1921 reported that the secretory pressure

5 Higgins, G. M., and Mann, F. C. Observations on the Emptying of the Gall Bladder, *Am J Physiol* **78** 339-348, 1926

6 Potter, J. C., and Mann, F. C. Pressure Changes in the Biliary Tract, *Am J M Sc* **171** 202-217, 1926

7 McMaster, P. D., and Elman, R. On the Expulsion of Bile by the Gall Bladder. Reciprocal Relationship with the Sphincter Activity, *J Exper Med* **44** 173-198, 1926

8 Ivy, A. C., and Oldberg, E. Hormone Mechanism for Gall Bladder Contraction and Evacuation, *Am J Physiol* **86** 599-613, 1928

9 Naunyn, B. Zur Naturgeschichte der Gallensteine und zur Cholelithiasis, *Mitt a d Grenzgeb d Med u Chir* **14** 537-554, 1905

10 Herring, P. T., and Simpson, S. The Pressure of Bile Secretion and the Mechanism of Bile Absorption in Obstruction of the Bile Duct, *Proc Roy Soc, London, s B* **79** 517-532, 1907

11 Mitchell, W. T., and Stifel, R. E. The Pressure of Bile Secretion During Chronic Obstruction of the Common Bile Duct, *Bull Johns Hopkins Hosp* **27** 78-79, 1916

12 Mann, F. C., and Foster, J. P. Secretory Pressure of the Liver, *Am J Physiol* **47** 278-282, 1918

13 Robitschek, W. and Turlot, M. Der Sekretionsdruck der Galle beim Menschen, *Wien klin Wchnschr* **34** 263 (June 2) 1921

of the bile varied in human patients from 210 to 270 mm. Koster, Shapiro and Lerner¹⁴ reported one case in which they found the normal tonus of the sphincter of Oddi to equal 230 mm of water. McGowan, Butsch and Walters¹⁵ were interested in changes in the pressure in the common bile duct, and in their experiments they did not attempt to determine the total pressure. However, they reported spasm of the sphincter of Oddi with an intensity equivalent to a pressure of over 600 mm of water. The pressure exerted by contraction of the human gallbladder has not been reported.

Cholangiography—The direct roentgenographic visualization of the biliary tree by the injection of iodized poppy-seed oil or some other roentgenopaque solution into a biliary fistula or into a drainage tube anchored in the gallbladder or bile ducts was introduced into clinical medicine by Lanari and Squirri¹⁶ in 1924. Immediate cholangiography or the visualization of the gallbladder or bile ducts at the time of operation was advocated by Mirizzi¹⁷. These methods have been extended and popularized by Ginzburg and Benjamin,¹⁸ Walters and Thiessen,¹⁹ Ross,²⁰ Hicken, Best and Hunt,²¹ Robins and Hermanson,²² and others. It is becoming generally accepted that cholangiography is a valuable diagnostic procedure in that it enables the presence of calculi, strictures or neoplasms or the course of a fistula affecting the biliary passages to be demonstrated visually and gives direct evidence

14 Koster, H., Shapiro, A., and Lerner, H. On the Rate of Secretion of Bile, *Am J Physiol* **115** 23-26, 1936

15 McGowan, J. M., Butsch, W. L., and Walters, W. Pressure in the Common Bile Duct of Man. Its Relation to Pain Following Cholecystectomy, *J A M A* **106** 2227-2230 (June 27) 1936

16 Lanari, E. L., and Squirri, C. M. Roentgenography of Biliary Passages After Lipiodol Injections, *Rev Asoc med argent* **37** 125-127, 1924

17 Mirizzi, P. L. La cholangiografia durante las operaciones de las vias biliares, *Progresos de la clin* **41** 213-221, 1933

18 Ginzburg, L., and Benjamin, E. W. Lipiodol Studies of Post-Operative Biliary Fistulae, *Ann Surg* **91** 233-241, 1930

19 Walters, W., and Thiessen, N. W. Visual Methods of Studying the Physiology of the Common Bile Duct. I. The Problem of Pancreatitis and Sphincteritis, *Proc Staff Meet., Mayo Clin* **9** 772-775 (Dec 19) 1934

20 Ross, J. C. The Use of Lipiodol in the Surgery of the Biliary Passages, *Lancet* **1** 251-254 (Feb 1) 1936

21 Hicken, N. F., Best, R. R., and Hunt, H. B. Cholangiography. Visualization of the Gall Bladder and Bile Ducts During and After Operation, *Ann Surg* **103** 210-229, 1936. Best, R. R., and Hicken, N. F. Cholangiographic Demonstration of Biliary Dyssynergia and Other Obstructive Lesions of the Gallbladder and Bile Ducts, *J A M A* **107** 1615-1619 (Nov 14) 1936

22 Robins, S. A., and Hermanson, L. Cholangiography. Modified Technique for X-Ray Visualization of Bile Ducts During Operation, *Surg., Gynec & Obst* **62** 684-688, 1936

regarding the patency of the biliary passages. In many patients, regardless of the presence of dilatation, infection of the bile ducts or calculi, the injected iodized oil passes into the duodenum without delay. In other cases there is retention of the oil in the biliary tree for periods up to three hours before it passes into the duodenum. This delay Best and Hicken,²³ and Hicken, Best and Hunt²¹ ascribe to spasm or hyper-tonicity of the choledochal sphincter, and in a series of seventy-five cases they found evidence of such spasm in 15 per cent.

One of the roentgenograms published by Saralegui²⁴ as illustrative of spasm of the sphincter is particularly interesting, for it shows the common duct filled with contrast medium. The ampulla of Vater is also filled with contrast medium, which extends up into the pancreatic ducts. The opening of the papilla of Vater is closed, though there is contrast medium in the duodenum. There seems to be a separate sphincter between the ampulla of Vater and the common duct. This roentgenogram, therefore, seems to indicate that the choledochal-duodenal sphincter really consists of two parts, and so is a most interesting confirmation of the views of Westphal²⁵ and Lueth²⁶.

The Clinical Syndromes Associated with Biliary Stasis—The demonstration by objective methods of increased tone or spasm of the choledochal sphincter is a development of the last few years, but the recognition of its importance in clinical medicine has come through clinical observations over a prolonged period. Krukenberg²⁷ in 1903 described the occurrence of biliary colic in the absence of gallstones. The extensive literature dealing with these functional disturbances was summarized by Ivy and Sandblom²⁸ in 1934. Ivy and Sandblom discussed the physiologic basis for the concept of functional disturbance or biliary dyskinesia.

The clinical syndromes produced by such dyskinesia have been discussed by Greene, Twiss and Carter²⁹ under the heading of biliary stasis. They pointed out that at least three types of disturbance produc-

23 Best, R. R., and Hicken, N. F. Biliary Dyssynergia. Physiological Obstruction of the Common Bile Duct, *Surg., Gynec. & Obst.* **61** 721-734, 1935.

24 Saralegui, J. A. Die Cholangiographien bei Studien der Gallenleiden [fig. 6], *Fortschr. a. d. Geb. d. Röntgenstrahlen* **52** 571-579, 1935.

25 Westphal, K. Muskelfunktion, Nervensystem und Pathologie der Gallenwege. I. Untersuchungen über den Schmerzanfall der Gallenwege und seine ausstrahlenden Reflexe, *Ztschr. f. klin. Med.* **96** 22-150, 1923.

26 Lueth, H. C. Studies on Flow of Bile into the Duodenum and Existence of Sphincter of Oddi, *Am. J. Physiol.* **99** 237-252, 1931.

27 Krukenberg, H. Ueber Gallenblasenkoliken ohne Gallenstein, *Berl. klin. Wchnschr.* **40** 667, 1903.

28 Ivy, A. C., and Sandblom, P. Biliary Dyskinesia, *Ann. Int. Med.* **8** 115-122, 1934.

29 Greene, C. H., Twiss, J. R., and Carter, R. F. Biliary Stasis. *Am. J. Digest. Dis. & Nutrition* **3** 622-624, 1936.

tive of stasis and an associated symptomatology can be recognized clinically. These types are of importance both in diagnosis and in treatment.

1 Obesity and a loss of muscle tone are observed in many women as the menopause is approached. Numerous observers have emphasized the increasing proportion of cases of achlorhydria that are observed in older persons. The presence of acid chyme in the duodenum not only causes relaxation of the sphincter of Oddi but stimulates evacuation of the gallbladder. Its absence in achlorhydria has the opposite effect, resulting in distention of the gallbladder. This may be referred to as atonic distention. The resultant biliary stasis is signaled clinically by epigastric or hypochondriac soreness or distress, which is most marked during fasting. Colic is infrequent. Achlorhydria or hypochlorhydria is shown by analysis of gastric contents. Gastro-intestinal roentgenograms usually show nothing abnormal. In the cholecystogram the shadow of the gallbladder appears distended and atonic. It may show delay in either filling or emptying. Duodenal drainage may procure a large quantity of concentrated bile, but frequently this is secured only after stimulation with olive oil. The biliary stasis is further shown by the presence of crystalline sediment. In such cases the condition responds to therapeutic management with a stimulating diet and the administration of hydrochloric acid, and a fatty diet or of olive oil between meals to stimulate evacuation of the gallbladder.

2 It has long been known that in many instances of duodenal ulcer the symptoms are those of disturbance of the gallbladder. In a further number of cases roentgen study of the gastro-intestinal tract shows duodenitis, periduodenal adhesions, pylorospasm, gastric ulcer and the like in association with disease of the gallbladder. In such cases it can be assumed that the increased motility and tone of the duodenal musculature and the sphincter of Oddi interfere with the normal evacuation of the gallbladder. Because there is an increased resistance to its emptying, the gallbladder becomes distended and hypertonic. This may be referred to as a hypertonic or spastic distention of the gallbladder. Clinically it is characterized by frequent attacks of colic, which may be accompanied by jaundice. Gastric hyperacidity usually is present. Roentgenograms of the gastro-intestinal tract show evidences of pylorospasm and spasm, hypermotility or increased tonus of the duodenal musculature. Cholecystograms show the gallbladder to be distended and hypertonic. Duodenal drainage shows evidence of stasis in the frequency in which concentrated bile is procured only after stimulation with olive oil. The bile is dark and concentrated, and the presence of crystalline sediment is further evidence of the stasis. In such cases the condition responds to therapeutic management with diets of the modified

ulcer type, antispasmodic drugs, such as belladonna, and alkalis to control the hyperacidity

3 The association of symptoms of disease of the gallbladder with neuroses of various types is no new observation. The association of chronic appendicitis, a spastic colon, pelvic disease or pregnancy with exacerbations of the symptoms of biliary stasis has been explained on a reflex basis. In such cases it may be assumed that there is a spasm of the sphincter of Oddi as a result of vagal stimulation which may arise directly in the central nervous system or reflexly in some other portion of the abdominal cavity. This spasm or increased tonus of the sphincter of Oddi interferes with the normal evacuation of the gallbladder which then becomes distended. This may be referred to as a neurogenic or vagotonic distention of the gallbladder. The resultant biliary stasis is characterized clinically by the presence of psychogenic factors or sources of reflex irritation which may explain the vagotonia. Biliary colic and even jaundice may occur. The gastric acidity is usually within the normal range, and gastro-intestinal roentgenograms do not show evidences of local lesions in the stomach or duodenum. Cholecystograms show the gallbladder to be distended, and hypertonic duodenal drainage shows evidence of stasis in the concentration of the bile and the presence of crystalline sediment. Concentrated bile, however, is usually obtained after stimulation with a solution of magnesium sulfate. In such cases the condition responds to therapeutic management with change of environment, mental rest, sedatives, antispasmodics and saline cathartics. It is this group in particular that is responsible for the vogue of "spa" therapy in the treatment of chronic cholecystitis.

The evaluation of the exact rôle of the individual factors of stasis, infection and metabolic changes in the production of disease of the gallbladder is difficult, but the concept of biliary stasis explains many of the clinical features of this disease. Failure to correct the stasis is responsible for many instances of recurrence of symptoms following cholecystectomy. Greene, Twiss and Carter pointed out that biliary stasis is not a single disease entity but may be the result of any one of various types of disturbance in the motor activity of the gallbladder and the biliary tract. They expressed the belief that these three main types at least can be recognized and that the recognition of them permits both a more accurate diagnosis and a more specific and satisfactory therapeutic management of the individual patient.

Pharmacologic Studies—The effectiveness of nitrites, glyceryl trinitrate and related compounds in producing vasodilatation is well known. Their action, however, is not limited to the smooth muscle of the blood vessels. The pharmacologic studies of Lieb and McWhorter³⁰ showed

30 Lieb, C. C., and McWhorter, J. E. Action of Drugs on the Isolated Gall-Bladder, *J. Pharmacol. & Exper. Therap.* 7: 83-98, 1915.

that they could produce relaxation of the gallbladder Beams³¹ stressed their value in clinical medicine in relieving cramps or spasm of the intestine Their value in producing relaxation of the sphincter of Oddi was shown by McGowan, Butsch and Walters and by Best and Hicken We can further testify as to the value of amyl nitrite or glyceryl trinitrate in relieving both biliary colic and pylorospasm

McGowan, Butsch and Walters¹⁵ reported studies on a series of cholecystectomized patients They were interested in changes in pressure in response to drugs rather than in the absolute values, so that their results cannot be compared directly with the data quoted previously However, they reported that a rise in the intraductal pressure was accompanied by pain The administration of morphine regularly produced a rise in pressure, and this was accompanied by pain The administration of amyl nitrite or of glyceryl trinitrate on the other hand rapidly brought the intraductal pressure down to zero, with relief of the pain These changes are most readily explained by the production of spasm of the sphincter of Oddi by morphine and the relief of this spasm by nitrites

These studies have been extended by McGowan, Butsch and Walters^{31a} and by Doubilet and Colp^{31b} They confirm the production of spasm of the sphincter of Oddi by therapeutic doses of morphine and dilauid A lesser degree of spasm was produced by pantopon (a mixture of the hydrochlorides of the opium alkaloids) or codeine Atropine or hyoscine caused a decrease in the tonus of the sphincter, but the spasm produced by morphine was relieved only by amyl nitrite or glyceryl trinitrate A few experiments also suggested that theophylline ethylene diamine had a relaxing effect Histamine, alcohol, ephedrine, epinephrine, papaverine, physostigmine, acetylcholine, ergotamine, calcium chloride, caffeine and phenobarbital in therapeutic doses had no distinct effect on the tonus of the sphincter

The increased knowledge of the physiology of the biliary tract accumulated during the past few years gives promise of adding new remedies to the list of those now used in the management of the biliary disorders

31 Beams, A J The Effect of Nitrites on Pain and on the Motility of the Gastro-Intestinal Tract I Clinical Study, *Arch Int Med* **49** 270-275 (Feb) 1932

31a McGowan, J M , Butsch, W L , and Walters, W The Use of Glyceryl Trinitrate (Nitroglycerine) for the Control of Pain Following Cholecystectomy, *Ann Surg* **104** 1013-1018, 1936 Butsch, W L , McGowan, J M , and Walters, W Clinical Studies on the Influence of Certain Drugs in Relation to Biliary Pain and to Variation in Intrabiliary Pressure, *Surg , Gynec & Obst* **63** 451-456, 1936

31b Doubilet, H , and Colp, R Resistance of the Sphincter of Oddi in the Human, *Surg , Gynec & Obst* **64** 622-633, 1937

Ergotamine tartrate has been introduced into internal medicine as a pharmacologic antagonist to epinephrine and has been used in depressing overactivity of the sympathetic nervous system. Lennox and von Storch,³² O'Sullivan³³ and several other investigators have found it of value in the relief of migraine. The pathogenesis of migraine is not known, though on an insecure basis it has been ascribed to hepatic disturbance. Similarly, the explanation of the action of ergotamine tartrate in relieving migraine is not clear. Ergotamine tartrate was also used successfully in treating the pruritus of jaundice by Lichtman,³⁴ Snell and Keyes³⁵ and others. The indiscriminate use of ergotamine tartrate is dangerous. Yater and Cahill³⁶ and Gould, Price and Ginsberg³⁷ each reported a case of bilateral gangrene of the feet following the use of large doses of ergotamine tartrate for the relief of pruritus in jaundice. Ergotamine may be of value in the treatment of the hypotonic type of biliary stasis, but it should be used with caution.

Choline and acetylcholine derivatives which stimulate the vagus or the parasympathetic nerve endings³⁸ likewise may be of value in the treatment of the hypotonic type of biliary stasis. The absorption of these two compounds after oral administration is variable, and they must be given hypodermically with caution because of the rapid but transitory fall of blood pressure which they produce. Acetylbetamethylcholine is now given by intranasal pack³⁹ or through the skin by ionto-

32 Lennox, W. G., and von Storch, T. J. C. Experience with Ergotamine Tartrate in One Hundred and Twenty Patients with Migraine, *J. A. M. A.* **105** 169-171 (July 20) 1935.

33 O'Sullivan, M. E. Termination of One Thousand Attacks of Migraine with Ergotamine Tartrate, *J. A. M. A.* **107** 1208-1212 (Oct. 10) 1936.

34 Lichtman, S. S. Therapeutic Response to Ergotamine Tartrate in Pruritus of Hepatic and Renal Origin, *J. A. M. A.* **97** 1463-1464, (Nov. 14) 1931.

35 Snell, A. M., and Keyes, H. C. Pruritus of Jaundiced Patients. Its Incidence and Treatment, *M. Clin. North America* **16** 1455-1470, 1933.

36 Yater, W. M., and Cahill, J. A. Bilateral Gangrene of Feet Due to Ergotamine Tartrate Used for Pruritus of Jaundice. Report of a Case Studied Arteriographically and Pathologically, *J. A. M. A.* **106** 1625-1631 (May 9) 1936.

37 Gould, S. E., Price, A. E., and Ginsberg, H. I. Gangrene and Death Following Ergotamine Tartrate (Gynergen) Therapy, *J. A. M. A.* **106** 1631-1635 (May 9) 1936.

38 Kovacs, J., Saylor, L. L., and Wright, I. S. The Pharmacological and Therapeutic Effects of Certain Choline Compounds, *Am. Heart J.* **11** 53-65, 1936. Myerson, A., Rinkel, M., and Dameshek, W. The Autonomic Pharmacology of the Gastric Juices, *New England J. Med.* **215** 1005-1013 (Nov. 26) 1936.

39 Van Dellen, T. R., Bruger, M., and Wright, I. S. The Absorption of Acetyl-B-Methylcholine Chloride (Mecholyl) by the Nasal Mucous Membrane, *J. Pharmacol. & Exper. Therap.*, to be published.

phoresis⁴⁰ Further experience is necessary to determine the value of this group of drugs in diseases of the biliary tract

Both ephedrine sulfate and benzedrine sulfate have been introduced into clinical medicine as sympatheticomimetic compounds which may be given orally⁴¹ Van Liere, Lough and Sleeth⁴² studied the effect of 1 grain (0.065 Gm) of ephedrine sulfate on the emptying time of the human stomach in six normal subjects Gastric evacuation was prolonged in all They expressed the opinion that ephedrine has two distinct actions on the stomach First, it may stimulate the sympathetic fibers, which would cause diminished motility, and second, it may actually relax the smooth muscle directly Myerson and Ritvo⁴³ found that benzedrine sulfate in doses of 30 mg by mouth is of great value in diminishing or abolishing spasm of the gastro-intestinal tract Gastric tonus was reduced slightly, but peristaltic action was not interrupted The stomach often emptied more rapidly after the administration of the drug because the relaxation of the pyloric sphincter allowed food to pass out of the stomach more rapidly than normally These two compounds are similar in their actions, nevertheless, they show slight but important differences in their effects It is possible that they will be of value in the treatment of spastic disturbances involving the biliary tract, but detailed studies have not been reported

Effect of Cholecystectomy—The experiments of Puestow⁴⁴ indicate that after cholecystectomy sphincteric tone is lost and bile dribbles into the duodenum as secreted The effect of cholecystectomy in abolishing the normal tone of the sphincter would seem to be transitory, for Potter and Mann found the pressure in the common duct to be increased after cholecystectomy in dogs, and Judd and Mann⁴⁵ reported that in dogs the common bile duct uniformly becomes dilated after cholecystectomy Puestow and Morrison⁴⁶ measured the circumference of the common

40 Kovacs, J The Iontophoresis of Acetyl-Beta-Methylcholine Chloride in the Treatment of Chronic Arthritis and Peripheral Vascular Disease Preliminary Report, Am J M Sc **188** 32-36, 1934

41 Myerson, A, Loman, J and Dameshek, W Physiologic Effects of Benzedrine and Its Relationship to Other Drugs Affecting the Autonomic Nervous System, Am J M Sc **192** 560, 1936

42 Van Liere, E J, Lough, D H, and Sleeth, C K The Effect of Ephedrine on the Emptying Time of the Human Stomach, J A M A **106** 535-536 (Feb 15) 1936

43 Myerson, A, and Ritvo, M Benzedrine Sulfate and Its Value in Spasm of the Gastro-Intestinal Tract, J A M A **107** 24-26 (July 4) 1936

44 Puestow, C B The Discharge of Bile into the Duodenum An Experimental Study, Arch Surg **23** 1013-1029 (Dec) 1931

45 Judd, E S, and Mann, F C The Effect of Removal of the Gall Bladder An Experimental Study, Surg, Gynec & Obst **24** 437-442, 1917

46 Puestow, C B, and Morrison, R B The Relationship of Cholecystitis and Cholecystectomy to Dilatation of the Choledochus, Ann Surg **101** 599-602, 1935

duct in a series of patients and found that while the presence of chronic cholecystitis with or without stones had little effect on the size of the common duct, cholecystectomy was followed by a considerable degree of dilatation. The gallbladder by virtue of its storage function serves to protect the common duct from the effects of increased pressure within the biliary tract, and the loss of this protection undoubtedly explains the increase in the frequency and severity of biliary colic observed in some patients after cholecystectomy.

Carter⁴⁷ discussed the importance of a study of the response of the sphincter of Oddi in those cases in which surgical drainage of the common duct is necessary. This is a procedure which is generally advocated for stones, cholangitis or chronic pancreatitis, but there has been no general agreement as to how long postoperative drainage is necessary. Ravdin stressed the importance of chemical and microscopic study of the bile as a guide to the persistence of infection and the severity of hepatic injury. Pribram,⁴⁸ Thorlakson and McMillan,⁴⁹ Walters and Thiessen and Hicken, Best and Hunt all pointed out that cholangiographic studies show that prolonged drainage of the common bile duct produces a reduction in the size of the dilated bile ducts, with a disappearance of the cholangiectasia. Carter admitted the importance of these different criteria of drainage but stressed the value of the food test. He measured the hourly drainage of bile during the day. When the sphincter of Oddi responds normally to food, the external drainage of bile is decreased or ceases entirely after meals. If the sphincter does not respond to food, the amount of biliary drainage is increased after the meal. A normal response to this food test indicates that the common duct is draining freely into the duodenum and the drainage tube in the common duct may safely be removed.

THE LIVER AND THE METABOLISM OF FAT

Fat Absorption—The importance of the bile in the absorption of fats has long been known. This is due partly to its action in activating the pancreatic lipase, partly to the action of the bile salts in favoring emulsification and solution of fats and so hastening lipolytic action and partly to the formation of soluble addition compounds of bile salts and fats or fat-soluble materials. These addition compounds are absorbed directly into the blood stream. The recent investigations of

47 Carter, R. F. When to Remove the Drainage Tube in Common Bile Duct Drainage, *Surg, Gynec & Obst* **63** 163-169, 1936.

48 Pribram, B. O. New Methods in Gall Stone Surgery, *Surg, Gynec & Obst* **60** 55-64, 1935.

49 Thorlakson, P. H., and McMillan, J. C. Common Duct Obstruction with Lipiodol Studies of Cholangiectasia Showing Effects of Prolonged Drainage, *Canad M A J* **31** 265-269, 1934.

Verzar⁵⁰ and of Drummond⁵¹ emphasizing the importance of bile in the absorption both of neutral fats and of fat-soluble materials were reviewed in 1936⁵² and need not be discussed in detail at the present time

The rate of absorption of fats is often mentioned in clinical literature as a valuable aid in the appraisal of the normal functioning of the liver. Sullivan and Fershtand⁵³ have studied the estimation of the degree of alimentary lipemia as an index of the rate of absorption of fat. Curves for absorption of fat by normal men and by patients with disease of the liver were obtained by following the changes in total fats of the serum subsequent to the ingestion of 100 Gm of cottonseed oil. Patients with definite disease of the liver showed a curve for absorption distinctly different from the normal and denoting a diminished and delayed absorption of ingested fat. This altered curve, based on values for fat in the blood, is deemed by the investigators sufficiently characteristic and different to be of aid in determining the functional status of the liver.

Although other reports support the use of this procedure in investigating the function of the liver, the results should be interpreted with caution. The quantity of fat in the blood at a given time is subject to the influence of a number of factors. The rate of uptake from the alimentary tract and the rate of deposition of the absorbed material in the cells of the body are important regulators of the level of blood fats. It should be remembered that lipemia occurs in association with diabetes as well as with starvation and does not, on the other hand, ordinarily develop in cases of chronic pancreatitis or carcinoma affecting other abdominal organs. These few instances of alteration of the blood fat levels unrelated directly to the functioning of the liver suffice to emphasize the limited importance that should be attached to absorption of fat, or alimentary lipemia, as a diagnostic measure of a hepatic condition.

Nachlas, Duff, Tidwell and Holt⁵⁴ attempted to avoid these difficulties by studying the lipemic curve after the intravenous administration

50 Verzar, F. Absorption of Fats, *Nutrition Abstr & Rev* **2** 441-450, 1933. Verzar, F, and Laszt, L. Studies on the Absorption of Fatty Acids, *Biochem Ztschr* **270** 24-35, 1934.

51 Drummond, J. C. Biochemical Studies of Liver Function in Relation to Fat Metabolism, in *Harvey Lectures, 1932-1933*, Baltimore, Johns Hopkins Press, 1934, pp 202-217.

52 Greene, C. H. Liver and Biliary Tract. A Review of Certain Recent Contributions, *Arch Int Med* **57** 1039-1054 (May) 1936.

53 Sullivan, M, and Fershtand, J. A. B. Fat Adsorption. Its Value as an Index of Function of the Liver, *Arch Int Med* **55** 834-841 (May) 1935.

54 Nachlas, A, Duff, G. L, Tidwell, H. C, and Holt, L. E. Liver Function as Tested by the Lipemic Curve After Intravenous Fat Administration, *J Clin Investigation* **15** 143-151, 1936.

of highly emulsified fat. They noted a rise in the curve for blood fat to a level above normal after the administration of carbon tetrachloride to dogs. A similar rise was found in one case of congenital malformation of the bile ducts. In consequence, they expressed the belief that this test is worthy of further clinical study.

Large amounts of fat are present in the stools of patients with obstructive jaundice. Muller⁵⁵ and Munk,⁵⁶ who made the first quantitative studies of this phase of fat metabolism, reported that the amount of fat lost in the feces varies up to 78 per cent of that included in the diet. It is now recognized that considerable quantities of lipid materials are excreted into the bowel, and in normal persons will account for the greater part of the fecal lipids. The increased excretion of fats in the stool in obstructive jaundice may be due to the presence of unabsorbed fat, to an increased excretion by the bowel or to a combination of these factors. In order to determine the origin of the fat in the feces of subjects with bile fistulas, Shapiro, Koster, Rittenberg and Schoenheimer⁵⁷ fed fat containing a known proportion of deuterium. This isotope of hydrogen apparently behaves as ordinary hydrogen in metabolism and yet can be quantitatively determined in compounds containing it. It therefore serves as an identifying "mark" for substances of which it is a part. The proportion of deuterium in the fecal fat equated with that in the fat ingested should thus serve as a reliable index to the origin of the fecal fat. It was found that of the deuterium-containing fat given with the food only 30 and 35 per cent, respectively, appeared in the feces of the two subjects studied. It was concluded from these analyses that the remaining 65 to 70 per cent of the fatty acids in the diet was absorbed and that the greater part of the fecal fat in these patients originated from the fat secreted into the intestinal tract. The subjects received 0.7 and 2.1 Gm of the deuterium-containing fat in the diet. It appears that such small amounts of fat can largely be absorbed even in the absence of bile. If all the food fat follows the course of the deuterium-containing fat, fecal lipid in the absence of bile is largely endogenous. If these conclusions can be confirmed, present day views regarding the degree of interference with absorption of fat produced by the absence of bile from the intestines should be modified.

The Intermediary Metabolism of Fats—After absorption from the intestine the fats are stored for the most part in the fat depots of the

55 Muller, F. Untersuchungen über den Icterus, *Ztschr f klin Med* **12**, 45-113, 1887.

56 Munk, J. Ueber die Resorption von Fetten usw nach Abschluss der Galle vom Darmkanal, *Virchows Arch f path Anat* **122** 302, 1890.

57 Shapiro, Arthur, Koster, Harry, Rittenberg, D., and Schoenheimer, R. The Origin of Fecal Fat in the Absence of Bile, Studied with Deuterium as an Indicator, *Am J Physiol* **117** 525-529 1936.

subcutaneous omental and retroperitoneal tissues. The fat is later withdrawn from these stores. The formation of unsaturated fatty acids from the saturated fats of the body has been looked on as one of the initial stages in the process of oxidation.

The studies of Burr and Burr⁵⁸ and of Evans and Lepovsky,⁵⁹ however, have shown that unsaturated fatty acids, such as linoleic and linolenic acid, are necessary for the growth of rats. Ellis and Isbell,⁶⁰ Ellis and Zeller⁶¹ and Banks and Hilditch⁶² likewise agreed that linoleic acid in the body is entirely exogenous in origin. This observation that linoleic and linolenic acids must be supplied in the diet is important if it can be confirmed in other species of animals besides the rat and pig, for it seems to indicate that the body is unable to desaturate fatty acids. Otherwise, these acids could readily be formed by the desaturation of oleic acid.

In the study of this problem, as in the study of many phases of intermediary metabolism, questions arise in which it would be desirable to distinguish between those molecules of a substance which come from the food and are exogenous and those which are formed in the body and are endogenous. Schoenheimer and Rittenberg⁶³ have attempted to mark molecules of fatty acid by the use of deuterium and so to follow the behavior of these marked molecules in the body. Unsaturated fats were saturated by hydrogenation with deuterium. The marked saturated fats were then fed to mice. At the completion of the experiment the animals were killed and the unsaturated fatty acids in the carcass were isolated. These unsaturated fatty acids contained an unduly high proportion of deuterium, showing that some were formed by the desatu-

58 Burr, G. O., and Burr, M. M. On the Nature and Role of the Fatty Acids Essential in Nutrition, *J. Biol. Chem.* **86** 587-621, 1930.

59 Evans, H. M., and Lepkovsky, S. Vital Need of the Body for Certain Unsaturated Fatty Acids. I. Experiments with Fat-Free Diets in Which Sucrose Furnishes the Sole Source of Energy, *J. Biol. Chem.* **96** 143-156, 1932. Vital Need of the Body for Certain Unsaturated Fatty Acids. II. Experiments with High Fat Diets in Which Saturated Fatty Acids Furnish the Sole Source of Energy, *ibid.* **96** 157-164, 1932.

60 Ellis, N. R., and Isbell, H. S. Soft Pork Studies. III. The Effect of Food Fat upon Body Fat, as Shown by the Separation of the Individual Fatty Acids of the Body Fat, *J. Biol. Chem.* **69** 239-248, 1926.

61 Ellis, N. R., and Zeller, J. H. Soft Pork Studies. IV. The Influence of a Ration Low in Fat upon the Composition of Body Fat of Hogs, *J. Biol. Chem.* **89** 185-197, 1930.

62 Banks, A., and Hilditch, T. P. The Body Fats of the Pig. II. Some Aspects of the Formation of Animal Depot Fats Suggested by the Composition of Their Glycerides and Fatty Acids, *Biochem. J.* **26** 298-309, 1932.

63 Schoenheimer, R., and Rittenberg, D. Deuterium as an Indicator in the Study of Intermediary Metabolism. V. The Desaturation of Fatty Acids in the Organism, *J. Biol. Chem.* **113** 505-510, 1936.

ration of the marked fat which had been fed. When unsaturated fatty acids labeled with deuterium were fed, the deuterium was later found in the saturated fatty acids obtained from the carcass.⁶⁴ These experiments therefore confirm in unmistakable fashion the older views that both the saturation and the unsaturation of fats take place in the body.

The older view of Leathes and Raper⁶⁵ insisted that the desaturation of fatty acids occurs in the liver. This theory was based on the observation that the fats in the liver usually are more unsaturated than those in the fat depots.

Various other explanations for this observation have been advanced, for the metabolism of unsaturated fats is not understood at the present time. Holt, Tidwell and Kirk⁶⁶ and Artom⁶⁷ found that they were better absorbed from the intestine than were saturated fats. Joannovics and Pick⁶⁸ showed that unsaturated fatty acids were selectively absorbed by the liver, and Sinclair⁶⁹ has shown recently that the liver not only selectively absorbs unsaturated fatty acids when cod liver oil is fed but retains them for a prolonged period.

The preferential absorption and retention by the liver of other fat-soluble materials, such as vitamin A, and some sterols, such as phytol, has been discussed by Drummond⁵¹ and by Davies and Moore.⁷⁰ Unsaturated fatty acids may be absorbed from the blood stream in the same fashion. The significance of these observations unfortunately is not yet clear, and further study of the rôle of the liver in the metabolism of fats is desirable.

64 Rittenberg, D., and Schoenheimer, R. Deuterium as an Indicator in the Study of Intermediary Metabolism. VIII. Hydrogenation of Fatty Acids in the Animal Organism, *J Biol Chem* **117** 485-490, 1937.

65 Leathes, J. B., and Raper, H. S. *The Fats*, New York, Longmans, Green & Co., 1925.

66 Holt, L. E., Tidwell, H. C., and Kirk, C. M. Studies on Fat Metabolism in Infants. *Acta paediat* **16** 165-176, 1933.

67 Artom, C. Fat Metabolism, in Luck, J. M. *Annual Review of Biochemistry*, Stanford University, Stanford University Press, 1935, vol. 4, p. 199.

68 Joannovics, G., and Pick, E. P. Experimentelle Untersuchungen über die Bedeutung der Leber bei der Fettresorption unter normalen und pathologischen Verhältnissen, *Wien klin Wchnschr* **23** 573, 1910.

69 Sinclair, R. G. Physiology of the Phospholipids, *Physiol Rev* **14** 351-403, 1934, *The Metabolism of the Phospholipids*. V. The Relationship Between the Amount of Fat Ingested and the Degree of Unsaturation of the Phospholipids and Neutral Fat in the Tissues of the Rat, *J Biol Chem* **96** 103-125, 1932, *The Metabolism of the Phospholipids*. IV. The Rate of Phospholipid Metabolism with Special Reference to the Question of the Intermediary Rôle of the Phospholipids in Fat Metabolism, *ibid* **95** 393-408, 1932.

70 Davies, A. W., and Moore, T. Vitamin A and Carotene. Elimination of Vitamin A from Livers of Rats Previously Given Massive Doses of Vitamin A Concentrate, *Biochem J* **29** 147-150, 1935.

It has been generally accepted that fats are burned by the process of β oxidation. Combustion normally is complete, but in various pathologic conditions associated with a deficient supply of carbohydrate oxidation is incomplete and ketosis results. The older work emphasizing the importance of the liver in the formation of ketone bodies has been summarized by Fischler⁷¹ and Snapper⁷². Confirmatory evidence has been introduced by Chaikoff and Soskin,⁷³ who showed that the ketone bodies in the blood of a depancreatized dog will fall rapidly after hepatectomy. Mirsky⁷⁴ confirmed the experiments of Anselmino and Hoffmann⁷⁵ showing that ketosis is produced in normal animals by the injection of the ketogenic principle of the anterior lobe of the hypophysis but further reported that ketosis did not follow the injection of this material in eviscerated rabbits. Himwich, Goldfarb and Weller⁷⁶ analyzed the arterial blood and the venous blood from various organs and found the liver to be the most constant source of ketone bodies.

The experiments of Jowett and Quastel,⁷⁷ Edson,⁷⁸ Trowell⁷⁹ and others also have shown that fatty acids are oxidized to aceto-acetic acid in vitro by slices of liver. More aceto-acetic acid was obtained by the oxidation of fatty acids with even-numbered carbon chains than by the

71 Fischler, F. *Physiologie und Pathologie der Leber nach ihrem heutigen Stande*, ed 2, Berlin, Julius Springer, 1925.

72 Snapper, I. Ueber den intermediären Stoffwechsel der Niere, *Verhandl d Gesellsch f Verdauungs -u Stoffwechselkr* **5** 92, 1925.

73 Chaikoff, I L, and Soskin, S. Utilization of Acetoacetic Acid by Normal and Diabetic Dogs Before and After Evisceration, *Am J Physiol* **87** 58-72, 1929.

74 Mirsky, I A. The Source of Blood Acetone Resulting from the Administration of the Ketogenic Principle of the Anterior Hypophysis, *Am J Physiol* **115** 424-428, 1936, Site and Mechanism of the Antiketogenic Action of Insulin, *ibid* **116** 322-326, 1936.

75 Anselmino, K J, and Hoffmann, F. Das Fettstoffwechsellhormon des Hypophysenvorderlappens. Nachweis, Darstellung und Eigenschaften des Hormons, *Klin Wchnschr* **10** 2380-2383, 1931.

76 Himwich, H E, Goldfarb, W, and Weller, A. The Effect of Various Organs on the Acetone Content of the Blood in Phlorhizin and Pancreatic Diabetes, *J Biol Chem* **93** 337-342, 1931.

77 Jowett, M, and Quastel, J H. Studies in Fat Metabolism. Oxidation of Butyric, Crotonic and B-Hydroxybutyric Acids in Presence of Guinea-Pig Liver Slices, *Biochem J* **29** 2143-2158, 1935, Studies in Fat Metabolism. Oxidation of Normal Saturated Fatty Acids in Presence of Liver Slices, *ibid* **29** 2159-2180, 1935, Studies in Fat Metabolism. Formation and Breakdown of Acetoacetic Acid in Animal Tissues, *ibid* **29** 2181-2191, 1935.

78 Edson, N L. Ketogenesis-Antiketogenesis. Influence of Ammonium Chloride on Ketone-Body Formation in Liver, *Biochem J* **29** 2082-2094, 1935.

79 Trowell, O A. Choline and Liver Respiration, *J Physiol* **85** 356-374 (Nov 22) 1935.

oxidation of those with an odd-numbered chain. This observation supports the old conception of β oxidation in the oxidation of fats, but in addition the possibility of there being other mechanisms whereby fat is oxidized must be kept in mind, for Quastel⁸⁰ found evidence for the oxidation of several other carbon atoms (multiple alternate oxidation). Verkade and van der Lee⁸¹ also found evidence for an additional ω oxidation.

These experiments stress the importance of the liver in the oxidation of fat. It must not be concluded, however, that this is necessarily a function of the liver exclusively, for McMaster and Drury⁸² showed that fat may be metabolized after hepatectomy.

Fatty Infiltration of the Liver—The amount of fat which can be visualized by histologic methods in an organ such as the liver does not necessarily correspond with the amount that can be determined by chemical analysis. This difference has been explained by the existence in protoplasm of lipoprotein complexes in which the fat does not take up the usual stains. The pathologist therefore is interested in fatty degeneration as evidence of cellular injury or destruction. The clinician, on the other hand, considers the liver the chief chemical factory of the body and is interested in the problem of fatty infiltration as evidence of the transport of fat to the liver as one step in its metabolism. The relationship between these two conditions has not yet been determined with certainty, but progress in the understanding of the rôle of the liver in the metabolism of fat is being made.

The clinical picture of fatty liver occurs in a great variety of conditions. In many of these, as in diabetic coma, the triad of Geelmuyden⁸³—mobilization of fat often with lipemia, fatty liver and ketonuria—is readily recognizable.

The clinical picture, however, is most variable, and many factors must be considered. Even in diabetes, enlargement of the liver with infiltration of fat may occur without associated ketonuria, as in the

80 Quastel, J. H. Oxidation of Fatty Acids in the Liver, *Arch f exper Zellforsch* **15** 57, 1934.

81 Verkade, P. E., and van der Lee, J. Researches on Fat Metabolism, *Biochem J* **28** 31-40, 1934, *Untersuchungen über den Fettstoffwechsel*, *Ztschr f physiol Chem* **225** 230-244, 1934, *Untersuchungen über den Fettstoffwechsel* Zweiseitige β -Oxydation der durch ω -Oxydation gesättigter Fettsäuren entstandenen Dicarbonsäuren, *ibid* **227** 213-222, 1934.

82 McMaster, P. D., and Drury, D. R. The Relation of the Liver to Fat Metabolism. I. Respiratory Quotient in Conditions of Liver Insufficiency, *Proc Soc Exper Biol & Med* **25** 151-153, 1927.

83 Geelmuyden, H. C. Ueber Fettwanderung, *Acta med Scandinav* **54** 5, 1920.

cases of Hanssen⁸⁴ Root⁸⁵ likewise reported four cases of diabetic coma with fatty liver Lipemia was observed in three, but in all four acute pancreatitis was present Bloom and Handelsman⁸⁶ reported a marked degree of fatty infiltration of the liver in a dog, with naturally occurring diabetes

Fatty infiltration of the liver can be produced in experimental animals under a variety of circumstances Fisher⁸⁷ and Allan, Bowie McLeod and Robinson⁸⁸ noted that in depancreatized dogs treated with insulin in adequate dosage there nevertheless developed marked fatty infiltration of the liver, which eventually resulted in the death of the animal The addition of raw pancreas to the diet prevented the development of the fatty liver McLeod likewise noted that this fatty infiltration of the liver could be prevented by the feeding of a fat-free extract of the pancreas Hershey and Soskin⁸⁹ found that lecithin can be substituted for the raw pancreas, though Ralli, Flaum and Banta⁹⁰ considered pancreas more effective than lecithin Finally, a study of the component parts of the lecithin molecule by Best, Ferguson and Hershey⁹¹ showed that the administration of choline would prevent the fatty infiltration of the liver in depancreatized dogs

These observations stimulated an extensive series of investigations dealing with fatty infiltration Feeding white rats a diet high in fat Best and Huntsman⁹² were able to produce fatty infiltration of the liver Diets rich in sugar and low in fat did not have this effect Best and Ridout⁹³ found that diets rich in cholesterol caused fatty liver,

84 Hanssen, P Enlargement of the Liver in Diabetes Mellitus, *J A M A* **106** 914-916 (March 14) 1936

85 Root, H F Diabetic Coma and Acute Pancreatitis with Fatty Livers, *J A M A* **108** 777-780 (March 6) 1937

86 Bloom, F, and Handelsman, M B Diabetes in Dogs, *North American Vet* **18** 39 (April) 1937

87 Fisher, N F Attempts to Maintain the Life of Totally Pancreatectomized Dogs, *Am J Physiol* **67** 634-643, 1924

88 Allan, F N, Bowie, J J, McLeod, J J R, and Robinson, W L Behaviour of Depancreatized Dogs Kept Alive with Insulin, *Brit J Exper Path* **5** 75-83, 1924-1925

89 Hershey, J M, and Soskin, S Substitution of "Lecithin" for Raw Pancreas in the Diet of the Depancreatized Dog, *Am J Physiol* **98** 74-85, 1931

90 Ralli, E, Flaum, G, and Banta, R J Results of Feeding Lecithin and Pancreas in Depancreatized Dogs on Liver Fat and Its Saponifiable and Unsaponifiable Fractions, *Am J Physiol* **110** 545-551, 1935

91 Best, C H, Ferguson, G C, and Hershey, J M Choline and Liver Fat in Diabetic Dogs, *J Physiol* **79** 94-102, 1933

92 Best, C H, and Huntsman, M E The Effects of the Components of Lecithin upon Deposition of Fat in the Liver, *J Physiol* **75** 405-412, 1932

93 Best, C H, and Ridout, J H Choline and Fatty Liver, *J Physiol* **84** 7P, 1935

and Blatherwick, Medlar, Bradshaw, Post and Sawyer⁹⁴ obtained similar results by feeding liver itself

The fatty deposits in the liver produced by a diet with a high fat content consists chiefly of neutral fats. According to Best, Channon and Ridout,⁹⁵ diets with a high cholesterol content produce an increase in both neutral fat and cholesterol, with a decrease in the phosphatide fraction. Channon and Wilkinson⁹⁶ found that the fat content of the liver increases more readily after the feeding of saturated fats than when unsaturated fats are fed. Kaplan and Chaikoff⁹⁷ also found that the fatty infiltration of the liver in depancreatized dogs is due to an increase in the neutral fats and to a lesser extent in cholesterol, with little or no change in the phosphatides.

In various papers Best⁹⁸ and his associates reported that choline reduces or prevents the fatty infiltration of the liver when high fat diets are fed. In reviewing the problem, Best stated that the administration of choline does not alter the rate of absorption of fat, nor does it affect the amount or character of the deposited fat, nor is there evidence at present that it increases the oxidation of fat in the liver. Best and Ridout showed that choline rapidly decreases the amount of neutral fat in the liver but only slowly reduces the accumulated cholesterol esters. Beeston, Channon and Loach^{98a} found that the addition of casein to a diet with a high fat content supplemented the effect of choline in preventing fatty infiltration.

Other methods of producing fatty infiltration of the liver have been studied. The fatty liver produced by starvation is well known. Dible and Libman⁹⁹ showed that the degree of infiltration is influenced by the nutritive state of the animal and that most marked changes do not occur unless large deposits of fat are present. Best and Ridout found

94 Blatherwick, N. R., Medlar, E. M., Bradshaw, P. J., Post, A. L., and Sawyer, S. D. Occurrence of Fatty Livers in Rats Fed Diets Containing Liver, *J. Biol. Chem.* **97** xxxiii, 1932.

95 Best, C. H., Channon, H. J., and Ridout, J. H. Choline and Dietary Production of Fatty Livers, *J. Physiol.* **81** 409-421 (July 31) 1934.

96 Channon, H. J., and Wilkinson, H. The Effect of Various Fats in the Production of Dietary Fatty Livers, *Biochem. J.* **30** 1033-1039, 1936.

97 Kaplan, A., and Chaikoff, I. L. Liver Lipids in Completely Depancreatized Dogs Maintained with Insulin, *J. Biol. Chem.* **108** 201-216, 1935.

98 Best, C. H. The Role of the Liver in the Metabolism of Carbohydrate and Fat. III. The Deposition of Liver Fat, *Lancet* **1** 1274-1277 (June 16) 1934.

98a Beeston, A. W., Channon, H. J., Loach, J. V., and Wilkinson, H. Further Observations of the Effect of Dietary Caseinogen in Prevention of Fatty Livers, *Biochem. J.* **30** 1040-1046, 1936.

99 Dible, J. H., and Libman, J. Further Observations on Fat Mobilization in Starvation, *J. Path. & Bact.* **38** 269-284, 1934.

that the effect of starvation on the liver was abolished by feeding choline for some weeks prior to the starvation period but that choline given during the period of starvation did not prevent fatty infiltration. Choline likewise diminished the amount of fat deposited in the liver after phosphorus poisoning, but according to Best, McLean and Ridout,¹⁰⁰ it did not reduce the toxicity of the phosphorus.

The posterior lobe of the pituitary gland influences fat metabolism, and this subject has been reviewed in detail by Raab.¹⁰¹ Mukerji and van Dyke¹⁰² reported that the fatty infiltration of the liver which follows a single injection of pitressin is not prevented by the administration of choline.

A new aspect of the aforementioned work has arisen with studies by Van Prohaska, Dragstedt and Harms¹⁰³ on the fatty infiltration of the livers of depancreatized dogs. They show that the changes in the liver were not due to the loss of the external pancreatic secretion, though Berg and Zucker¹⁰⁴ previously had reported that damage to the liver followed the production of a pancreatic fistula. Von Prohaska and his associates¹⁰⁵ demonstrated further that the small amount of raw pancreas needed to prevent the changes in the liver contained such a small amount of choline or lecithin that these constituents could not have been responsible for its effect in preventing fatty infiltration. Dragstedt, Van Prohaska and Harms later isolated a fat-free alcohol-soluble substance from the pancreas, which they called the "lipocaine hormone." When fed to dogs this material prevented the liver from becoming infiltrated with fat. These authors found that depancreatized dogs still required the substance after hypophysectomy despite improvement in the dietary status. This new work brings up the necessity of further study of the action of choline in its relation to the pancreatic hormone.

100 Best, C. H., McLean, D. L., and Ridout, J. H. Choline and Liver Fat in Phosphorus Poisoning, *J. Physiol.* **83** 275-284 (Feb. 9) 1935.

101 Raab, W. The Role of the Pituitary Posterior Hormone in Fat Metabolism, *Endocrinology* **14** 385-388, 1930.

102 Mukerji, B., and van Dyke, H. B. The Effect of the Pressor Principle of the Posterior Lobe of the Pituitary Body on the Liver-Fat After the Feeding of Choline Chloride, *Chinese J. Physiol.* **9** 69-76, 1935.

103 Dragstedt, L. R., Van Prohaska, J., and Harms, H. P. Observations on a Substance in Pancreas Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, *Am. J. Physiol.* **117** 175-181, 1936.

104 Berg, B. N., and Zucker, T. F. Liver Changes After Deprivation of External Pancreatic Secretion, *Proc. Soc. Exper. Biol. & Med.* **29** 68-70, 1931.

105 Van Prohaska, J., Dragstedt, L., and Harms, H. P. The Relation of Pancreatic Juice to the Fatty Infiltration and Degeneration of the Liver in the Depancreatized Dog, *Am. J. Physiol.* **117** 166-174, 1936.

Kaplan and Chaikoff¹⁰⁶ have studied the size and composition of the liver of a normal dog and of dogs under a variety of abnormal conditions, including depancreatized, hypophysectomized, hypophysectomized-depancreatized, phlorhizin-treated and thyroid-fed animals. The composition of the liver varied widely in these different conditions. However, the absolute amount of water and protein in the liver was relatively constant and was not affected by changes in the amount of either glycogen or fat.

These results suggest that the absolute amount of the active functioning protoplasm of the liver does not change in such acute experiments and that the changes in fat or glycogen represent the addition or subtraction of reserves which only indirectly affect the activity of the living protoplasm. The experiments of Addis, Poo and Lew¹⁰⁷ supplement these studies by indicating that so far as protein is concerned the liver may also be a storage depot for use in time of need.

This point of view is particularly important, since a great many previous experiments have been interpreted as showing not only that the deposition of glycogen in the liver is associated with the retention of considerable amounts of water but that there is also a considerable antagonism between the deposition of glycogen and that of fat. Nagao,¹⁰⁸ for example, found that the intravenous injection of fat produces a deposition of fat associated with disappearance of glycogen from the liver.

It has been recognized previously that depancreatized dogs show an increase in dextrose-tolerance when fatty infiltration of the liver occurs. Best, Huntsman and Young,¹⁰⁹ on the other hand, insisted that the apparent increase in the sugar tolerance in these dogs antedates the deposition in fat in the liver and that instead of there being an antagonistic relationship between the glycogen and fat of the liver, the derangement of both phases of metabolism is due to the same cause, a disturbed hepatic function which affects first the metabolism of sugar and later the metabolism of fat. These questions are of direct clinical importance with regard to both the causation and the significance of fatty infiltration of the liver, and it is hoped that definitive experiments which answer some of these questions conclusively will soon be reported.

106 Kaplan, A., and Chaikoff, I. L. The Relation of Glycogen, Fat, and Protein to Water Storage in the Liver, *J Biol Chem* **116** 663-682, 1936

107 Addis, T., Poo, L. J., and Lew, W. Protein Loss from Liver During a Two Day Fast, *J Biol Chem* **115** 117-118, 1936

108 Nagao, S. The Penetration of Glycogen and Fat into the Parenchyma as Antagonistic Processes, *Tohoku J Exper Med* **24** 555-564, 1934

109 Best, C. H., Huntsman, M. E., and Young, F. G. The Effect of Diets Low in Choline, and of Choline Feeding, on the Glycosuria of the Depancreatized Dog, *J Physiol* **85** 8P, 1935

THE METABOLISM OF AMINO-ACIDS AND AMMONIA IN
DISEASE OF THE LIVER

The importance of the liver in protein metabolism has been repeatedly and conclusively demonstrated Kirk¹¹⁰ has recently reported the study of the metabolism of amino-acids and ammonia in a series of fifty-seven cases of hepatic disease. As part of the study, he discussed the analytic difficulties in the determination of these materials and furnished good reasons for disregarding most of the published data bearing on this problem. He found that the aminonitrogen in the plasma varies over the same range in patients with disease of the liver as in normal persons. Curves for tolerance obtained by administering 25 Gm of amino-acetic acid likewise fell within the normal range. Analysis of urine both after fasting and after administration of 25 Gm of amino-acetic acid showed that the excretion of aminonitrogen was the same in normal persons as in patients with hepatic disease. He therefore concluded that in his experiments an impairment of the mechanism for deaminizing aminoacids could not be demonstrated. The clinical value of tolerance tests with amino-acetic acid was questioned accordingly.

The concentration of ammonia in the blood normally is low, varying from 0.013 to 0.050 mg per hundred cubic centimeters. Normal values were obtained in hepatic disease, with the exception of cirrhosis. In cirrhosis, on the other hand, the fasting concentration was increased, and it increased even more remarkably after the administration of ammonium citrate. Kirk reported additional evidence indicating that the ability to synthesize urea from ammonia was unimpaired. The concentration of ammonia in the blood of the portal vein is much greater than that in the peripheral blood stream, but the ammonia normally is almost completely removed by the liver. In persons with hepatic cirrhosis, who have a well developed collateral circulation, enough portal blood is shunted around the liver to affect the concentration of ammonia in the peripheral blood stream. Kirk therefore concluded that the determination of the ammonia in the blood in cirrhosis affords no information regarding the functional state of the liver but does furnish a method for studying the development of collateral circulation in such a case.

SYPHILIS OF THE LIVER

The many and varied types of hepatic lesion that have been ascribed to syphilitic infection were reviewed by O'Leary, Greene and Rowntree¹¹¹ in 1929. The gumma is the one hepatic lesion that is universally

110 Kirk, E. Amino Acid and Ammonia Metabolism in Liver Diseases, Copenhagen, Levin & Munksgaard, 1936.

111 O'Leary, P. A., Greene, C. H., and Rowntree, L. G. Diseases of the Liver. VIII. The Various Types of Syphilis of the Liver with Reference to Tests for Hepatic Function, *Arch Int Med* **44** 155-193 (Aug) 1929.

accepted as being syphilitic in origin, but it seems probable that syphilitic disturbances of the liver are far more frequent than would be indicated by the incidence of hepatic gumma

Biskind, Epstein, and Kerr¹¹² in 1934 reported a study of the bengal rose test for hepatic function in a series of one hundred and fifty-two syphilitic persons. After excluding all those in whom there was clinical evidence of hepatic involvement, they reported that functional disturbance could be demonstrated in over 17 per cent. Similar results were reported in 1936 by Kellogg, Epstein and Kerr¹¹³. These results are most important if they can be confirmed by other methods, for they indicate a frequency of hepatic injury far higher than is usually accepted.

A detailed survey of the literature, with especial reference to the factors responsible for jaundice in syphilis, was reported by Sager¹¹⁴ with particular reference to the rôle of arsphenamine. He reported that transient slight jaundice is occasionally found in syphilitic cirrhosis or in gumma of the liver, but the clinical syndrome of acute yellow atrophy is not found in association with tertiary syphilis.

Acute jaundice associated with the secondary stage of syphilis, the icterus syphiliticus praecox, was the only type recognized in the pre-arsphenamine era. Sager suggested that this type of jaundice in untreated persons with secondary syphilis is caused by parenchymatous hepatic injury produced by the toxemia associated with systemic invasion by the spirochete. It apparently is not due to an inflammatory response of the liver to the presence of the spirochete.

Jaundice has been observed in syphilitic persons with increasing frequency since the introduction of arsphenamine. This increase has been noted both in secondary and in tertiary syphilis. Experimentally, arsphenamine damages the liver, and jaundice may be produced in dogs by large doses. The incidence of jaundice increases with the drug used. Jaundice also occurs after the therapeutic use of arsphenamine in non-syphilitic persons. Other reactions caused by arsphenamine, such as arsphenamine dermatitis, occasionally appear with the jaundice. Sager therefore concluded that arsphenamine is the toxic agent responsible for the development of paratherapeutic or postarsphenamine jaundice.

112 Biskind, G. R., Epstein, N. N., and Kerr, W. J. Hepatic Complications in the Treatment of Syphilis. The Rose Bengal Test as a Means of Detecting Disturbances of Liver Function and Its Use as a Guide in the Therapy of Syphilis, *Ann Int Med* **7** 966-980, 1934.

113 Kellogg, F., Epstein, N. N., and Kerr, W. J. Hepatic Complications in the Treatment of Syphilis. II. Incidence of Hepatic Disease in Patients with Untreated Syphilis and During Their Subsequent Treatment, *Ann Int Med* **9** 1561-1571, 1936.

114 Sager, R. V. Factors Responsible for Jaundice in Syphilis with Special Reference to the Rôle of the Arsphenamines, *Arch Int Med* **57** 666-694 (April) 1936.

and that this type of jaundice is a separate etiologic variety distinct from the usual varieties of catarrhal jaundice

THE TREATMENT OF HEPATIC DISEASE

The treatment of hepatic disease is neither fully understood nor appreciated by the medical profession as a whole. Treatment in general can be divided into four main divisions: (1) general care of the patient apart from the disease of the liver, (2) the treatment of parenchymal injury, (3) the treatment of ascites and (4) symptomatic treatment for the relief of specific symptoms.

General Care—The general care of the patient apart from the disease of the liver is an individual question and need not be reviewed at this time.

The Treatment of Parenchymal Injury—1 Dextrose. The agents which may damage the liver are varied in the extreme, and no attempt will be made to catalog them. There are ample experimental data as well as corroborative clinical evidence that a supply of glycogen is essential to the normal functioning of the liver. When adequate reserves of glycogen are present, not only is the liver more resistant to injury but regeneration and the restoration of normal function are more rapid than when these reserves are depleted. The glycogen supply of the liver is normally built up from the carbohydrate in the food.¹¹⁵ Such experiments as those of Tsai,¹¹⁶ Butsch,¹¹⁷ Salter, Robb and Scharles¹¹⁸ show that glycogen is formed equally well from dextrose given by vein and from that administered orally. London,¹¹⁹ Tsai and Yi,¹²⁰ Olmsted and Reed¹²¹ and Giragossintz and Olmsted,¹²² on the

115 Bollman, J. L., and Mann, F. C. Experimentally Produced Lesions of the Liver, *Ann Int Med* **5** 699-712, 1931. Ivy, A. C. and Crandall, L. A. Liver and Bile, in Luck, J. M. Annual Review of Biochemistry, Stanford University, Stanford University Press, 1936, vol. 5, pp. 427-447.

116 Tsai, C. Carbohydrate Metabolism of Liver. Glycogen and Other Carbohydrates in Decapitate Cats, *Chinese J Physiol* **7** 215-226 (Dec 15) 1933.

117 Butsch, W. L. Glucose Tolerance and the Glycogen Storage Capacity of the Dog, *Am J Physiol* **108** 639-642, 1934.

118 Salter, W. T., Robb, P. D., and Scharles, F. H. Liver Glycogen from Derivatives of Glucose, *J Nutrition* **9** 11-23, 1935.

119 London, E. S. Agiostomie und Organstoffwechsel, Moscow, Des All-Union-Instituts fur exper Med, 1935.

120 Tsai, C., and Yi, C. L. Carbohydrate Metabolism of Liver. Sugar Output in Amytalized Cats, *Chinese J Physiol* **8** 399-408 (Nov 15) 1934.

121 Olmsted, J. M. D., and Reed, L. S. Glucose and Non-Glucose Portions of "Blood Sugar" in the Hepatic and Portal Veins of the Decapitate Cat at Different Sugar Levels, *Am J Physiol* **109** 303-306, 1934.

122 Giragossintz, G., and Olmsted, J. M. D. Portal and Hepatic Blood Sugar After Glucose Administration, *Proc Soc Exper Biol & Med* **32** 668-670, 1935.

other hand, found that the dextrose content of the blood from the hepatic vein is greater than that of blood from the portal vein even at times when glycogen is being deposited in the liver. These results seem to indicate that glycogenolysis by the liver and the liberation of dextrose into the hepatic veins are a continuous process. These investigators suggest that the hepatic glycogen may not be formed directly from the dextrose in the blood but from some other glycogenic substance.

Experience has demonstrated that an ample intake of carbohydrate ordinarily will result in the deposition of glycogen in the liver. A high carbohydrate diet therefore is indicated in the treatment of acute injury of the liver and is usually used in jaundice. When the patient is able to eat, there is no reason why the carbohydrate should not be administered orally in a high carbohydrate diet. The general rule in such cases,^{122a} as exemplified by the reports of Althausen¹²³ and Jones,¹²⁴ is to supply between 300 and 500 Gm of carbohydrate. When the patient cannot eat such a diet, other methods of supplying carbohydrate must be sought. When weakness, anorexia or coma make feeding unsatisfactory, tube feeding should be tried. When a duodenal tube can be put in place, the administration of liquids in a continuous drip is most satisfactory.

Enemas of dextrose have not been satisfactory in our hands, for after the initial trial they are poorly retained and cause much discomfort.

A 5 per cent solution of dextrose may be given by hypodermoclysis, but the total amount which may be given in this way is small, and unless the patient is badly dehydrated the dextrose is accompanied by an unduly large volume of water. The intravenous infusion of a solution of dextrose in concentrations of from 10 to 25 per cent has come to be the method of choice for supplying it to the patient with acute disease of the liver.

The continuous intravenous infusion of a solution of dextrose as reported by Hendon¹²⁵ and others is occasionally of value. Technical difficulties, particularly with regard to preventing thrombosis or occlusion of the vein, however, militate against its use except under special conditions.

It has been suggested that whenever a solution of dextrose is administered intravenously insulin should be given to insure the utiliza-

122a Martin, L. Jaundice. *Methods of Diagnosis and Treatment of Its Causes*, Bull. Johns Hopkins Hosp. **59** 78-98, 1936.

123 Althausen, T. L. Dextrose Therapy in Diseases of the Liver, *J. A. M. A.* **100** 1163-1167 (April 15) 1933.

124 Jones, C. M. The Treatment of Acute Hepatic Insufficiency and Its Relation to Prognosis, *Am. J. Digest. Dis. & Nutrition* **3** 624-629, 1936.

125 Hendon, G. A. Experiences with Venoclysis, *Ann. Surg.* **91** 753-760, 1930.

tion of the dextrose Our experience has indicated that except in diabetic patients little dextrose is excreted in the urine after its intravenous administration This loss is reduced but not abolished by the simultaneous injection of insulin, and it may be concluded that the insulinogenic function of the pancreas is unimpaired in the great majority of patients with hepatic disease In fact, Althausen warns that the continuous intravenous injection of dextrose should be decreased gradually and not stopped abruptly, because of the danger of insulin shock in consequence of the stimulation of production of insulin by the dextrose

2 Protein in the Diet Meat and meat extracts should be eliminated from the diet of all patients with severe hepatic disease The danger of meat intoxication in dogs with an Eck fistula was emphasized by Fishler Bollman and Mann pointed out that dogs on a high meat diet showed more extensive necrosis of the liver after carbon tetrachloride poisoning than did dogs on a high carbohydrate diet Furthermore, they pointed out that in dogs with severe hepatic injury the development of ascites can be precipitated by the administration of meat or meat extracts

The protein intake should not be restricted too rigidly One of us (C H G⁵²) reviewed the evidence indicating that the liver is active in the formation of the serum protein and pointed out that evidences of a reduction in the serum protein or a change in the albumin-globulin ratio or both was found in many patient's with hepatic disease The majority of papers have stressed the toxicity of meat rather than that of protein We therefore doubt the advisability of reducing the protein in the diet below 1 Gm per kilogram of body weight, especially if that protein is given in the form of eggs and milk or dairy products

The palatability of the diet is important, especially when it is necessary for the patient to follow a prescribed regimen for a prolonged period Meat is most valuable in affecting the palatability of the diet, and we believe that many patients with cirrhosis follow their diet better if small amounts of meat are allowed occasionally

3 Fat in the Diet If large amounts of carbohydrate are given in the diet, the fat will automatically be reduced Many physicians believe that a fat-free diet is essential However, butter and cream and egg yolks usually are well tolerated by the patient with hepatic disease and need not be eliminated from the diet, even though they do supply a modicum of fat

Hepatic injury or jaundice induced by arsphenamine represents a special group Craven¹²⁶ has shown that when dogs kept on a high

126 Craven, E B The Importance of Diet in Preventing Acute Yellow Atrophy During Arsphenamine Treatment, *Bull Johns Hopkins Hosp* 48 131-142, 1931

fat diet are given arsphenamine there is less hepatic necrosis than in dogs on a high carbohydrate diet. It is to be hoped that this question will be reinvestigated in detail and the applicability of these studies to patients be proved. Cross and Blackford¹²⁷ have shown the development of severe hypoglycemia in subacute yellow atrophy of the liver secondary to administration of arsphenamine. The indications for the selection of a high fat or a high carbohydrate diet in such cases are not clear at the present time.

4 Calcium Therapy. The experiments of Minot and of Cutler¹²⁸ have shown that the hepatic necrosis of carbon tetrachloride poisoning in dogs may be diminished by the administration of both calcium and dextrose. Part of the benefit observed may be due to the action of calcium in neutralizing the effect of guanidine and related compounds, which are toxic and part to a hastening of glycogenolysis.

Most interesting are the recent experiments of Forbes, Neale and Scherer¹²⁹ dealing with the isolation of a compound of commercial liver extracts which protects the liver from the toxic effects of carbon tetrachloride.

The Treatment of Ascites—The medical management of ascites is primarily a problem of the effective use of diuretics, a topic which has been thoroughly reviewed by Hayman¹³⁰ and by Keith¹³¹. They pointed out that the diuretics of greatest value in the treatment of ascites are mercurial compounds, acid-producing or potassium salts and purine diuretics.

The Addison pill of ancient lineage, containing digitalis, squill and mercury, is still a popular diuretic for the treatment of ascites, but the greatest usefulness is found in organic compounds of mercury, such as merbaphen, salyrgan and mercurin (the sodium salt of trimethylcyclopentane-dicarboxylic acid-methoxymercuryhydroxydeallylamide).

Numerous organic mercurial diuretics have been reported, but accumulated clinical experience indicates that of the group described salyrgan and mercurin have the greatest diuretic effect and produce minimal toxic symptoms. The usual practice is to give 0.5 cc intra-

127 Cross, J. B., and Blackford, L. M. Fatal Hepatogenic Hypoglycemia Following Neoarsphenamine, *J. A. M. A.* **94** 1739-1742 (May 31) 1930.

128 Cutler, J. T. The Influence of Diet on Carbon Tetrachloride Intoxication in Dogs, *J. Pharmacol. & Exper. Therap.* **45** 209-226, 1932.

129 Forbes, J. C., Neale, R. C., and Scherer, J. H. A Liver Preparation Protecting Against Necrosis from Chloroform or Carbon Tetrachloride Administration, *J. Pharmacol. & Exper. Therap.* **58** 402-408, 1936.

130 Hayman, J. M. The Clinical Use of Diuretics, *J. A. M. A.* **107** 1937-1941 (Dec 12) 1936.

131 Keith, N. M. The Action and Use of Diuretics with Especial Reference to Mercurial Compounds, *J. A. M. A.* **107** 2047-2051 (Dec 19) 1936.

venously as an initial trial dose. If there are no toxic effects, 2 cc is given every three or four days as long as there is a satisfactory diuretic response. The mercurial compounds are irritating, and care must be used in making the injection, else there is danger of subcutaneous necrosis. They may be given intramuscularly, but this method of administration is usually painful and not as satisfactory as the intravenous route. Recently both mercurin and salyrgan have been supplied in suppositories for rectal administration containing 0.5 Gm of the mercurial salt. Parkinson and Thomson,¹³² Fulton,¹³³ Flexner¹³⁴ and others have reported satisfactory diuretic response to the use of such suppositories, especially in cases of cardiac edema.

Mercurial diuretics are contraindicated or should be used with extreme caution in acute nephritis or in the presence of renal insufficiency with incipient uremia. When used with discretion and care in properly selected cases, they may be given over long periods without any evidence of renal injury. However, the possibility of renal injury should not be forgotten, and the physician must be on the lookout for evidences of its appearance. This danger is not eliminated by the introduction of the mercurial suppository, for one of us (C. H. G.) has observed a case in which temporary anuria resulted from the administration of a mercurin suppository.

The various inorganic acid-producing salts have a moderate diuretic action of their own, but they show an even more striking effect in augmenting the diuretic action of the organic mercurial compounds. The most effective acid salts have been ammonium chloride and ammonium nitrate. Keith has also stressed the value of potassium nitrate. Large doses of these various compounds are required, the recommended daily dose being ammonium chloride 9 Gm, ammonium nitrate 12 Gm and potassium nitrate 12 Gm. They all are irritant to the stomach and may produce vomiting, so they are best administered at meal time in 0.5 Gm enteric-coated pills. The most marked acidifying effect of ammonium chloride is of relatively short duration, being greatest on the second and third days of administration. It is therefore best given intermittently—as on the first three days of the week. If the mercurial compound is given less frequently, the acid salt should be administered for two days before and throughout the day the mercurial compound is injected.

The purine or xanthine diuretics, theophylline, theobromine and caffeine or their derivatives, usually are effective in the order named. They are of less importance in the treatment of ascites due to portal

132 Parkinson, J, and Thomson, W. A. R. A Mercurial (Nouvurit) Suppository as a Diuretic for Cardiac Edema, *Lancet* **1** 16-19 (Jan 4) 1936.

133 Fulton, M. N. Mercurin Suppositories as a Diuretic in the Treatment of Edema. *New England J Med* **214** 1092-1095 (May 28) 1936.

134 Flexner, I. Personal communication to the authors.

cirrhosis than they are in cardiac diopsy. However, there is some evidence that they enhance the effectiveness of the mercurial compounds.

Hayman also reported that urea may be an effective diuretic in ascites.

It is generally agreed that the most dramatic response to the therapeutic use of diuretic drugs occurs in cases of congestive heart failure. They are effective in many cases of early portal cirrhosis, but the more advanced the hepatic insufficiency the less the response to diuresis. In our experience, some patients respond well to a diuretic regimen but as time and presumably the severity of the lesion progress the response lessens and finally disappears. The ascites occasionally noted in acute hepatitis likewise responds poorly to treatment with diuretics.

Many investigators have suggested that the liver is active in water metabolism, and the aforementioned observations suggest that diuresis is less easily produced, as the functional efficiency of the liver is reduced. This view is also supported by the observations of Jones and Eaton¹³⁵ regarding the good prognostic significance of spontaneous diuresis in hepatic disease. Most patients with cirrhosis with ascites should be on a salt-poor diet, and the fluid intake should be moderately restricted, say to 1,000 to 1,200 cc. The advantages of more rigid restriction are usually counterbalanced by the unpalatability of the required diet and the consequent loss of appetite.

Purgation formerly was much used in the management of ascites. The modern view is to relegate this type of therapy to the discard, for the benefit is not sufficient to counterbalance the many and obvious disadvantages.

Paracentesis remains the measure of last resort in the management of ascites. Frequent tapping should be avoided if possible, for much protein is lost in the ascitic fluid, and this loss not only increases the nutritional disturbance but hastens the depletion of the plasma proteins, a circumstance which carried to an extreme will produce peripheral edema and, in lesser degree, undoubtedly favor the production of ascites. The patient with a distended, fluid-filled abdomen on the other hand is much more comfortable and subjectively feels much better if the excess of fluid is removed by paracentesis and diuretics are used to prevent or delay its reaccumulation than if an attempt is made to treat the condition solely by medical measures.

Symptomatic Treatment for the Relief of Specific Symptoms—A multitude of individual symptoms that require care and attention on the part of the physician are observed in cases of hepatic disease. Only a few of the more important ones will be referred to here.

¹³⁵ Jones, C. M., and Eaton, F. B. The Prognostic Significance of a Spontaneous Diuresis in Acute or Subacute Disease of the Liver, *New England J. Med.* **213** 907-918 (Nov. 7) 1935.

1 Anemia The occurrence in cases of severe hepatic disease of macrocytic hyperchromic anemia with a blood picture resembling that seen in pernicious anemia was discussed previously Further reports have been published during the year in confirmation of these observations Shumacker and Wintrobe,¹³⁶ and Higgins and Stasney¹³⁷ also reported the experimental production of macrocytic anemia in dogs in which severe and long continued hepatic damage and cirrhosis had been produced by the administration of carbon tetrachloride Fortunately this anemia ordinarily responds to the parenteral administration of liver extract, and such therapy is indicated in any case of hepatic disease in which there are evidences of an increase in the color index or a change in the volume of the erythrocytes

2 Serum Proteins The serum proteins frequently are reduced in portal cirrhosis In most cases there is a deficiency in serum albumin, with a tendency toward an inversion of the albumin-globulin ratio

The Takata-Ara test and similar tests produce positive reactions Three factors contribute to the development of these changes interference with the production of the serum proteins by the damaged liver, the depletion of serum proteins as a result of loss of protein through frequent tapping and the withdrawal of large amounts of ascitic fluid, a reduction in the protein intake as a result of either restriction of protein in the diet or anorexia or other digestive disturbance which prevents the intake or utilization of protein

The reports of Foley, Keeton, Kendrick and Darling,¹³⁸ O'Hare and Driscoll,¹³⁹ and Myers and Keefer¹⁴⁰ emphasize these different factors but show that inanition or a deficient protein intake will produce a reduction in the plasma proteins without change in the albumin-globulin ratio The reduction in the plasma proteins may be combated in part by a careful increase in the protein in the diet, though the response usually is disappointing There usually is no direct relationship between the reduction in the plasma proteins and the loss in the ascitic fluid These investigators agree that the degree of hypoproteinemia tends to

136 Shumacker, H B, and Wintrobe, M M Morphologic Changes in Blood Associated with Experimentally Produced Hepatic Damage, *Bull Johns Hopkins Hosp* **58** 343-377, 1936

137 Higgins, G, and Stasney, J Peripheral Blood in Experimental Cirrhosis of Liver, *Folia haemat* **54** 129-144, 1936

138 Foley, E F, Keeton, R W, Kendrick, A B, and Darling, D Alterations in Serum Proteins as an Index of Liver Failure, *Proc Soc Exper Biol & Med* **33** 430-431, 1935

139 O'Hare, J P, and Driscoll, M Blood Proteins in Liver Disease, in *Medical Papers Dedicated to Henry Asbury Christian, Physician and Teacher, in Honor of His Sixtieth Birthday*, Baltimore, Waverly Press, Inc, 1936, p 638

140 Myers, W, and Keefer, C Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of Liver, *Arch Int Med* **55** 349-359 (March) 1935

be proportional to the degree of cirrhosis and express the belief that it is the consequence of a diminished production of plasma proteins by the damaged liver. Treatment therefore is best directed toward combating the hepatic injury. In other cases, transfusion is indicated for its value in supplying both erythrocytes and plasma proteins.

3 Pruritus. Pruritus, which is one of the most disturbing symptoms of the patient with hepatic disease, has been discussed by Snell and Keyes. The patient with obstructive jaundice often has most dramatic relief after the reestablishment of the flow of bile. On the other hand, the patient with cirrhosis or chronic hepatitis who has pruritus presents a therapeutic problem of the first magnitude. Ergotamine tartrate, already referred to, may be of great benefit. The intravenous administration of sodium thiosulfate in 1 Gm. doses sometimes produces equally great relief, as may calcium gluconate administered intravenously. Small doses of histamine subcutaneously have been used by Ernstene and Banks¹⁴¹ in the treatment of pruritus of urticarial origin. One of us (A. M. B.) has used it successfully for two patients with jaundice. Duodenal drainage or mild mercurous chloride at times seems to stimulate the flow of bile sufficiently to reduce the intensity of the itching. Diathermy may help. Local measures, such as bran or soda baths or lotions or salves containing phenol or local anesthetics, usually give but transient benefit. There seems to be no sure way of telling in advance which of these measures will relieve any individual patient. While the search is being made, the patient should be given sedatives in sufficiently large doses to secure rest and a modicum of comfort.

¹⁴¹ Ernstene, A. C., and Banks, B. M. Use of Histamine in the Treatment of Pruritus. Preliminary Report, *J. A. M. A.* **100** 328-330 (Feb. 4) 1933.

Book Reviews

Collected Writings By Alfred F Hess Price, \$15 Pp 1443, with 127 illustrations Springfield, Ill Charles C Thomas, Publisher, 1936

To those who long knew and loved the man, who appreciated the fertility and the versatility of his mind, who were familiar with his work as it appeared and who looked forward eagerly to each new development, it is still a revelation to scan the 1,400 pages of the two volume "Collected Writings" of Alfred Hess. After a foreword by Mrs Hess and a sympathetic biographic memoir by his friend Abraham Flexner in collaboration with E A Park, there are in chronological order nearly 200 papers, with 43 omitted "in order that the volumes should not be too cumbersome"

The work is a marvelous record of achievement dominated by a personality that was in many ways unique. It is no mere posthumous tribute when Park says that Hess was "the foremost investigator among pediatricians in this country. There was no one else who could possibly be compared with him. He was probably the foremost pediatric investigator in the world." And yet, paradoxically, as Flexner says in his memoir "Hess was not really a master of any special method of investigation. He was not a bacteriologist, a chemist, a histologist or a physiologist. Without complete equipment, therefore, in any of the underlying sciences he was nevertheless one of the very foremost investigators of his time in medicine. One might add that he was not an outstanding clinician in the usual sense. As revealed in these collected writings, he combined and made all these special technics subservient to a method that was peculiarly his own. This has been admirably stated by Park. "Hess was a great skirmisher on the forefront of scientific progress, with an almost uncanny eye for the point at which the next attack should be made, with a genius for predicting the course which investigation should take, with almost infallible judgment on the basis of slight evidence and simple experiment as to where the weak point in the armor of ignorance lay. It was fortunate that a man with this scouting sense was not held back to command a regular body of troops. He blazed many paths, leaving other workers less daring and less imaginative to complete the work, while he passed on to other points of vantage."

This is evident in the chronological sequence of his work as shown in these volumes. A line of investigation was taken up and followed for a time and either seen to a conclusion or, after the way had been pointed, left to others to pursue into farther ramifications. As a result, one can roughly divide Hess' work into epochs. Beginning with a single case report and historical summary, he rapidly entered on a period of intensive interest in contagious diseases, notably tuberculosis. This was overlapped by the introduction of the duodenal catheter, with important demonstrations as to the pathogenesis of the hard casein curds in the stools of infants and the nature and flora of the pancreatic juice, and opened up wide avenues to further investigation. This subject was abruptly dropped because, as Hess characteristically told this reviewer, he "was no longer interested in going on with it—others could do that." There followed a short period of investigation into the nature of the disorders of the blood and of capillary resistance, leading to the demonstration, since confirmed by Aschoff and Wolbach, that the hemorrhages of infantile scurvy are due to the pathologic permeability of the capillaries. From that time on his great work, with a few deviations, dealt with deficiency diseases. First came a brilliant series of reports on the nature, pathogenesis and therapy of infantile scurvy. This again was all but terminated when his comprehensive book entitled "Scurvy, Past and Present" appeared in 1920. With the exception of some illuminating reports on vitamin A and dental caries, nearly all his later investigations centered on rickets, his outstanding single achievement. Discovery after discovery, not by chance but by the use of that

"almost uncanny eye for the point at which the next attack should be made," followed in rapid succession, among the most far reaching being the discovery that inert substances can be made incredibly rich in vitamin D by ultraviolet irradiation. Again there came a comprehensive summary in a book published in 1929 entitled "Rickets, Osteomalacia and Tetany," about which Finkelstein wrote him "There has been no medical book in many years which has fascinated me so much and has given me so much pleasure and such edification in equal measure by its content and form" Much has been added to our knowledge of the vitamin D complex since that time, and the last 350 pages of the "Collected Writings" are an eloquent record of Hess' further contributions to that subject. His wise counsel and mature judgment, both leading and restraining, were never needed more, in this connection, than at the present time. It is a pity that Nature is at times so lavish and so ruthless. These volumes are a fitting memorial to the great and lovable personality—a stimulating reminder to future generations of students of medicine.

Synopsis of Clinical Laboratory Methods By W. E. Bray, M.D. Price, \$3.75. Pp. 324, with 32 illustrations and 11 color plates. St. Louis: C. V. Mosby Company, 1936.

This book consists of sixteen chapters which cover with few exceptions those clinical laboratory procedures that are simple and of proved clinical value.

The first chapter discusses in a general way the procedures that are part of the routine of the various hospital services or which may be needed on special indication. It gives a bird's-eye view of the equipment and tests necessary in each particular field.

The second chapter is a clear and complete presentation of the routine and special examinations that may be made of a specimen of urine. The Addison count, however, is omitted. The third chapter deals with hematology and is followed by chapters on blood chemistry, gastric analysis, feces analysis, intestinal parasites, examination of the cerebrospinal and other puncture fluids and examination of sputum. Throughout these chapters the methods of greatest simplicity have been critically selected, and any method which sacrifices reasonable accuracy to obtain simplicity has been deleted. Wherever possible the apparatus required is that which may be found in a laboratory not overly elaborate and expensively equipped.

The chapter on bacteriology is as concise and inclusive a fifty page treatise on the detection of pathogenic micro-organisms as one can conceive.

The chapter on water and milk analysis is only four pages long, and while necessarily incomplete for any one especially interested in this field, it probably gives sufficient information to make a satisfactory determination of the purity of these two liquids.

The chapter on serology is concerned entirely with the complement fixation, flocculation and precipitin tests for syphilis and is up to the uniformly high standard of the rest of the book. The Kolmer modification of the Wassermann test and the Kahn and Kline tests are recommended.

The chapters on basal metabolism and allergy tests are very short (two and three pages, respectively), and while they give considerable information in such a brief space, additional reading in these fields would be necessary to equip one to derive the best results from these procedures. The chapter on poisons and foreign substances is one that under ordinary circumstances will not be needed often but if needed at all will be badly needed. The detection of ordinary poisons is here clearly described.

The chapter on surgical pathology would of course require special training and much additional study and practice to be of much value to most physicians. Possibly it should have been omitted. The last chapter is composed of methods of preparation of over one hundred indicators, stains and reagents. Twenty-five random tests of the index proved it to be 100 per cent correct.

This book meets all the requirements of simplicity, clearness, accuracy and completeness that one could possibly lay down. It is written not for the research worker but for the medical student, for the laboratory technician and for the physician who is keeping abreast of the times and ever doing his best to practice modern medicine. It fulfills its purpose admirably and is hereby recommended to those who come within the scope of its declared purpose.

Glandular Physiology and Therapy A Symposium Prepared Under the Auspices of the Council on Pharmacy and Chemistry of the American Medical Association. Cloth. Price, \$2.50. Pp 528. Chicago: American Medical Association, 1935.

There would be no great exaggeration in saying that all proved facts concerning glandular physiology and therapy are contained in this volume. The tone of this book is definitely conservative, and it is refreshing, indeed, to read a book on this subject in which the limitations and ignorance in the well populated field of endocrinology are so frankly admitted.

Scholarly papers set forth the results of well controlled laboratory work, and the success or failure of the clinical application of this work is ably discussed by competent clinicians.

It is surprising that it seemed necessary to devote nearly a fourth of the book to a discussion of the pituitary gland, but this was a wise procedure in view of the extensive amount of work recently accomplished in this field together with the seemingly unwarranted enthusiasm on the part of clinicians to tamper with the pituitary gland.

The gonads receive adequate attention, including an interesting but speculative chapter on carcinogenesis. A discussion of tests for pregnancy is included in this section.

The adrenal glands, thyroid and parathyroid glands, thymus and pancreas, including insulin therapy, are considered from a physiologic and clinical standpoint.

Gastro-intestinal principles are discussed, together with the antianemic material from the liver and stomach.

In the final chapter commercial glandular preparations are considered, and mention by name is made of commercial preparations that are thought to have value. The preparations are described together with the bases for their probable value. Mention is made also, but not by name, of preparations that are probably valueless. This chapter should be read with attention by every physician who prescribes glandular preparations.

It is more than likely that the enthusiastic but uncritical reader will consider this work far too conservative, but conservatism is needed today in endocrinology as well as in other fields.

Differentialdiagnose in der inneren Medizin By O. Naegeli, M.D. Price, 9.60 marks. Pp 216, with 61 illustrations. Leipzig: Georg Thieme, 1936.

This volume is the first of three which will represent the complete work of Naegeli on differential diagnosis in internal medicine. The second part is scheduled to appear in 1936 and the third in 1937, the total representing approximately 700 or 800 pages. This volume is short, containing 216 pages, and is paper bound.

Instead of approaching differential diagnosis from the standpoint of symptoms alone, Naegeli prefers to proceed from a broad point of view, first identifying the disease as an inflammation, intoxication, tumor, lymphatic or allied disorder, endocrine disturbance, allergic state, avitaminosis, deficiency disease or involvement of an isolated organ, such as the heart or brain. A brief discussion of each of these groups is given. For example under inflammation the various criteria to establish such a diagnosis, such as the temperature, pulse rate, sedimentation time of the blood and leukocytic responses, are evaluated. The author then

plunges into a consideration of the differential diagnosis in specific groups. First, the anemias are considered and then polycythemia, the hemorrhagic diatheses, leukemias, disorders of the lymph nodes, mediastinal tumors, disturbances of the salivary glands, myelopathies, ulcerative lesions of the mouth, splenic disorders and disturbances of the liver and biliary tract.

Under each heading the important factors in differential diagnosis are stressed. The more important differentiations are taken up in relation to the symptom complex, such as isolated afebrile splenic tumor, enlargement of the lymph nodes and ulcerative lesions of the mouth. Frequent case reports illustrate the diagnostic procedure and problems at hand.

The work represents an approach to differential diagnosis that is seldom seen in English works. One is impressed by the absence of long lists of rare causes of usual symptoms and delighted to see an approach to differential diagnosis as it is practiced at the bedside. The book should find its place as a practical guide to the problems of differential diagnosis.

Food and Beverage Analyses By Milton A. Bridges. Price, \$3.50. Pp. 246. Philadelphia: Lea & Febiger, 1935.

Thirty years ago the investigations of Atwater and Bryant were published as Bulletin 28 of the United States Department of Agriculture, and this work has been a classic in the realm of nutrition, having been utilized all over the world. Since then practically nothing has been written of any moment concerning the analysis of foods, and this in spite of the fact that a host of new foods in various forms have been presented to the eating public.

Bridges has made an enormous number of original food analyses and in addition has had made an extensive search of international data in order to collect in one volume the information presented in this book. The result is an extremely complete summary of every known article of diet, at least any unusual article of food which the reviewer, picking at random, attempted to find absent was listed.

The arrangement of the material is such that the inquirer may refer to a given article with a minimum of trouble. The size of a portion of each article is given both in grams and in household measurements, and then the relative amount of carbohydrate, protein and fat, together with the total number of calories. The table of foods makes up the bulk of the book, but there are also sections devoted to the mineral content of food and to their vitamin value. One section deals with the composition and food values of alcoholic beverages, and one can find there just what is contained in a "Merry Widow" or a "Soul Kiss" cocktail as well as how to mix a slow gin fizz, make a mint julep or concoct a planter's punch.

This volume represents a tremendous amount of work, it presents to nutritionist, dietitian and physician accurate information conveniently arranged. It is difficult to see how the physician can get along without it.

Basal Metabolism in Health and Disease By Eugene F. Du Bois, M.D. Third edition. Cloth. Price, \$5. Pp. 494, with 98 engravings. Philadelphia: Lea & Febiger, 1936.

Du Bois has correlated the investigations of pure science with the clinical problems of human metabolism. He begins with the related fundamentals of physics and biochemistry, creates an understanding of the interplay of forces defining and controlling normal metabolism and then discusses the pathologic physiology of metabolism in disease. These progressive steps are of great value to the student or to the practitioner whose knowledge of the fundamental sciences is limited, vague or out of date. No attempt is made to apply data difficult of interpretation to the gaps in one's knowledge of metabolism. Most of the information catalogued is acceptable when tested by present day methods and thinkers.

The third edition of this book contains recent information on surface area and normal standards and incorporates work done by J. D. Hardy, using a new type

of radiometer to study loss of heat. The discussion of undernutrition, obesity and allied states in diabetes provides the basis for intelligent dietary treatment of these conditions. The chapter on the thyroid gland is exceptionally well organized. The incomplete and contradictory state of the literature on the adrenal, pituitary and sex glands and their interrelationship has made metabolic studies of these conditions of little practical value. The chapters on diseases of the blood and on diseases of the heart and kidneys could be more adequately correlated with the pathologic physiology of these conditions. Water metabolism might be discussed in more detail. However, despite these few criticisms the volume may be heartily recommended. It presents authoritative information on metabolism in the language of the student and the clinician.

Endokrine Krankheiten By Prof. Dr. Hans Curschmann, Direktor d. Medizin Univ. Klinik i. M. With a contribution by Dr. med. et phil. Franz Prange, Nervenarzt in Rostock. **Medizinische Praxis, Band I**. Second Revised Edition. Price, unbound, 8 marks, bound, 9 marks. Pp. 144, with 47 illustrations. Dresden: Theodor Steinkopff, 1936.

This book is an abbreviation of the standard German texts on endocrinology and is especially rich in photographs of patients. The accounts are brief and accurate, but it is regrettable that in a book primarily for practitioners there should be inadequate discussion of certain elementary principles of therapy. The indications for surgical procedure and the proper preoperative use of iodine in cases of exophthalmic goiter are hardly touched on, the importance of sodium in adrenal insufficiency is not mentioned at all, and there is no adequate discussion of the essential chemical changes in hyperparathyroidism.

Grundriss der inneren Medizin By Dr. A. von Domarus. Tenth edition. Price, 16.80 marks. Pp. 681, with 63 illustrations. Berlin: Julius Springer, 1936.

The number of editions through which this work has gone in its thirteen years of existence speaks not only for its popularity but for the keen interest of the author and publisher in keeping it up to date. Now in its tenth edition, it maintains a compactness and conciseness essential for student and quick reference use. True to the word *Grundriss* the discussions of the various disease states are brief. Tuberculosis, for example, is covered in eight pages and brucellosis in less than three. Essential facts, however, are not omitted, and discussions of controversial subjects are evaded. References are rarely given. The general plan and style of previous editions are maintained.

Die einheimische Sprue By Dr. K. Hansen and Dr. H. von Staa. Price, 7.80 marks. Pp. 113, with 45 illustrations. Leipzig: Georg Thieme, 1936.

This excellent monograph, beautifully illustrated and with an extensive bibliography, covers the subject of endemic sprue. There are interesting reports of cases, and the question of the relation of this condition to idiopathic steatorrhea and osteomalacia is analyzed.

CLINICAL USE OF EXTRACT OF THE ADRENAL CORTEX

REPORT ON THIRTYFOUR CASES OF ADDISON'S DISEASE STUDIED
BETWEEN 1930 AND 1937, WITH A REVIEW OF
THE LITERATURE

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The recognition of the functions of the various endocrine glands and of the importance of the hormones which they produce is one of the recent developments in medicine. The adrenal glands, for example, were described by Eustachius in 1563, but nearly three hundred years elapsed before there was any real insight into their physiologic activity. In 1855 Addison pointed out the constitutional effects of disease of these glands and established the clinical syndrome which bears his name. The experiments of Oliver and Schafer in 1895 paved the way for the isolation and chemical identification of epinephrine by Abel and Takamine a few years later.

The last-mentioned discovery focused attention on the medullary portion of the adrenal gland, and the majority of subsequent investigations have dealt with the functional activity of the medulla. Other experiments, however, have been concerned with the effects of partial or complete extirpation of these glands. These experiments, the results of which have recently been summarized by Britton, established beyond question the uniformly fatal effect of total adrenalectomy in practically all laboratory animals. They have further emphasized the preponderant rôle of the cortical portion of the gland in the maintenance of life after partial adrenalectomy. Epinephrine is ineffective in maintaining life in such animals, and efforts to isolate the active principle or principles from the adrenal cortex were unsuccessful for a long time. Banting and Garms, Rogoff and Stewart, Hartman and his associates and many others made pioneer investigations in this field, but the first evidence that the life of a totally adrenalectomized cat can be prolonged indefinitely by the administration of an extract of the adrenal cortex was presented in 1930 by Swingle and Pfiffner. Hartman and Brownell, working independently of these investigators, reported similar results.

From the Department of Medicine, the New York Post-Graduate Medical School and Hospital

a few weeks later. These workers used lipid solvents for the extraction of the active principle.

The activity of extracts prepared in this manner has been confirmed by numerous investigators, and it is now recognized that totally adrenalectomized animals can be kept alive and in a state of normal health for an indefinite period by the continuous administration of adrenal extracts. Numerous recent investigators, among whom may be mentioned Swingle and Pfiffner, Grollman and Firor, Zwemer, Zwemer, Agate and Schroeder, and Pfiffner, Vars and Taylor, have reported the preparation of purified extracts of great potency, while Kendall and his associates have described the crystallization of an active principle. It is probable, therefore, that in the near future the chemical structure of the cortical hormone will be determined and that the purified product will become available for general use in therapy. Consequently, it is fitting to review the experience with the use of the present cruder extracts, so that it may be determined in what fields of medicine the purified product is likely to be of greatest usefulness.

Reference should be made to various comprehensive reviews, such as those of Britton, Swingle and Pfiffner, Harrop and Haitman, for a discussion of the effects of total adrenalectomy in experimental animals and of the response of such animals to the administration of a cortical extract. No certain criterion of the degree of adrenal insufficiency has been described. The ability of an extract to maintain a totally adrenalectomized animal in a state of health indefinitely is still the final test of its potency. Swingle and Pfiffner in 1932 made the following statement, which is still valid:

The real functional significance of the cortical hormone is unknown. All of the changes reported as occurring in the organism following bilateral adrenalectomy, we regard as secondary to some at present unknown, underlying derangement of the animal. The literature is filled with theories and hypotheses of adrenal function.

No one has yet succeeded in presenting definite, clear-cut, unequivocal evidence of cortical function. The function of the adrenal cortex is a subtle and intriguing one, but the solution is not yet at hand.

Adrenal cortex extract has been used most frequently and with most dramatic results in the treatment of Addison's disease. Certain features of the clinical course of this disease must be kept in mind in considering the effects of treatment. Addison's disease, as shown in the tabulation of Guttman, is almost always due either to bilateral tuberculosis or to bilateral contraction (cortical atrophy) of the adrenal glands. The proportion of cases in which tuberculosis is present varies, depending on the series cited, from 70 to 85 per cent of the total number. The course of the disease usually is of progressively increasing severity. In occasional cases the condition may be stationary for a long time, as in the instance (reported by Snell) in which the patient had been under observation for seventeen years. Sooner or later, how-

ever, there is acute exacerbatation, with crisis and death. The disease is usually rapidly fatal. In 88 cases in which no treatment was given, selected from the records of the Mayo Clinic, the average length of life was one and eighty-two hundredths years, and in half of the cases the patient died within one and twenty-seven hundredths years. The duration of life in 266 cases in which there was no treatment is given in the accompanying table. This table includes data on the 88 cases from the Mayo Clinic and 178 cases the reports of which were compiled by Guttman. It shows that only 71.4 per cent of the total number of patients lived more than six months, 51.3 per cent more than one year and 10.5 per cent four years after the onset of definite symptoms.

*Results of Observations in Cases of Addison's Disease Showing Comparative Duration of Illness in 34 Cases Studied from 1930 to 1937 in Which Treatment with Adrenal Extract Was Given and in 266 Cases in Which No Treatment Was Given**

Period of Survival of Patients	Percentage of Patients Who Survived	
	Patients Receiving No Treatment	Patients Receiving Treatment
6 months or more	71.4	88.2
1 year or more	51.3	67.6
1½ years or more	36.5	55.8
2 years or more	31.2	49.9
2½ years or more	20.7	44.0
3 years or more	18.4	38.1
3½ years or more	11.3	35.2
4 years or more	10.5	29.3
4½ years or more		23.5
5 years or more	7.5	
5½ years or more	6.4	
6 years or more	5.6	18.8
8 years or more	4.5	
10 years or more	1.5	14.1

* Prof. W. W. Swingle, of Princeton University, and Dr. Oliver Kamm, of Parke, Davis & Company, furnished supplies of extract which made the initial treatment of these patients possible. The work of Swingle and Pfiffner was aided in part by a grant from the Josiah Macy Jr. Foundation.

The clinical course in the usual case of Addison's disease, as pointed out by Greene, Rowntree, Swingle and Pfiffner, may be divided into three periods:

1. The period of initial destruction of the adrenal glands or latent adrenal insufficiency. Both the clinical and the experimental observations indicate that the adrenal glands possess considerable functional reserve. Clinically recognizable signs of adrenal insufficiency, or Addison's disease, do not appear until this reserve is seriously impaired or destroyed.

2. The period of the recognized clinical syndrome or partial adrenal insufficiency. The characteristic clinical symptoms of Addison's disease, namely, asthenia, pigmentation, loss of weight and strength and arterial hypotension, are well known. Once they appear, the diagnosis is established. In cases in which the diagnosis is doubtful, the roentgeno-

graphic demonstration of calcification of the adrenal glands, as pointed out by Ball, Greene, Camp and Rowntree and by Camp, Ball and Greene, is evidence of tuberculosis of the adrenals and so is of value in confirming the diagnosis

3 The terminal period of crisis or total adrenal insufficiency Patients with Addison's disease ordinarily have little resistance, even to the ordinary stress and strain of every-day existence Intercurrent infection, exposure to cold or high temperatures, undue fatigue, whether physical or mental, gastro-intestinal disturbance, too active purgation, the unwise administration of drugs, such as insulin or thyroid extract, and minor trauma or operation, such as dental extraction or tonsillectomy, frequently serve as predisposing factors to initiate an acute condition resembling shock or a period of crisis This condition is characterized by severe gastro-intestinal disturbance, nausea, vomiting, dehydration, pain, nervous irritability, circulatory collapse, low blood pressure, cold extremities, reduction in the output of urine and lowered body temperature In the secondary stage, the basal metabolic rate may be reduced, and the sugar content of the blood is frequently low In the period of crisis, these changes are more marked In addition, hemoconcentration is high, the blood volume is reduced, and the viscosity of the blood is increased The hemoglobin concentration, the urea and nonprotein nitrogen contents of the blood and the protein, calcium, potassium and inorganic sulfate contents of the serum are increased The alkali reserve, the chloride content and, as Loeb pointed out, the sodium content of the serum are reduced The similarity between the condition of a patient in the crisis of Addison's disease and that of a laboratory animal after complete adrenalectomy and the resemblance of both these states to the condition of surgical shock have been pointed out many times (Greene, Rowntree, Swingle and Pfiffner, Harrop, Sullivan, MacLean and Zwemer, and Swingle, Pfiffner, Vars, Bott and Parkins)

TREATMENT OF ADDISON'S DISEASE

The successful treatment of Addison's disease is difficult and calls on the resourcefulness of the physician to the fullest extent It should be directed along four main lines (1) treatment of the underlying disease, (2) protection of the patient, (3) symptomatic therapy and (4) specific organotherapy

Treatment of the Underlying Disease—Since in the majority of cases Addison's disease is due to tuberculosis, the problem of treatment of this disease is primarily the problem of the treatment of tuberculosis It is, indeed, fortunate that involvement of the adrenals is so infrequent in tuberculosis The cause of cortical atrophy is generally thought

to be unknown, so that therapy is difficult. Warthin, on the other hand, insisted that in many cases Addison's disease is due to latent syphilis. If this is correct, specific therapy is possible. Frank syphilis, though of infrequent occurrence, is perhaps the third most common cause of adrenal insufficiency in Addison's disease.

Protection of the Patient—The sensitivity of the patient with a mild or moderate degree of adrenal insufficiency to the ordinary stress and strain of daily life and the ease and suddenness with which crisis may be precipitated have been mentioned. To avoid such an accident, the patient should be protected in every way possible. The danger of intercurrent infection, physical and mental fatigue and exhaustion, gastrointestinal disturbance, exposure to low or high temperatures or unwise medication and the importance of protection against such mishaps or, when they are unavoidable, of early and active treatment cannot be stressed too strongly.

Symptomatic Therapy with Particular Reference to Anhydremia and Shock—Anhydremia and shock dominate the clinical picture both in a patient in crisis and in an experimental animal after complete adrenalectomy. Whether this is due to a primary function of the adrenal cortex in the regulation of the metabolism of water and salts, as claimed by Zwemer, Loeb, Harrop, and Swingle, Pfiffner, Vars, Bott and Parkins, or whether the condition is secondary to some yet uncharacterized function of the gland is perhaps an academic question. The value of injections of physiologic solution of sodium chloride or of Ringer's solution in prolonging the life of adrenalectomized animals has been recognized since the work of Soddu. The value of infusions of saline solution or of 10 per cent dextrose in physiologic solution of sodium chloride in the treatment of patients in crisis, as pointed out by Rowntree, Greene, Swingle and Pfiffner, was recognized before active adrenal extracts were available for clinical use. This is illustrated in the case reported by Wakefield, as well as in the cases recently described by Loeb and Harrop. I have seen several patients with Addison's disease who did not do well, even though sufficient fluid and saline solution were given to prevent dehydration and depletion of salt, and who improved when adrenal extract was given in addition. A similar case has recently been reported by Kincov, Zillessen and Rowntree. On the other hand, many patients with Addison's disease report a craving for salty food-stuffs, such as sauerkraut, ham, pickles and tomatoes with salt. One such youth ate salt with as much relish as a child eats sugar. The provision of an adequate intake of fluids and salt is essential to the management of Addison's disease.

During the past two years, abundant evidence cited by Loeb, Atchley and Stahl, Loeb, Harrop, Kepler, and others has been produced to

show that both adrenalectomized animals and patients with Addison's disease do better with an ample intake of sodium. Conversely, a reduction in the intake of sodium may precipitate a crisis of adrenal insufficiency and so be of diagnostic value in a case in which the diagnosis is doubtful.

Allers, Nilson and Kendall, Wilder and his associates, Allott, and Zwemer and Truszkowski have emphasized the harmful effects of retention of potassium in adrenalectomized animals and in patients with Addison's disease. Not only does the clinical condition of the patient show a closer correlation with the degree of retention of potassium than with the loss of sodium but in dogs the administration of potassium will precipitate a crisis of acute adrenal insufficiency. The most beneficial effects of an increased intake of sodium are not obtained in patients unless the intake of potassium salts is limited.

Specific Organotherapy—Organotherapy is as old as the clinical recognition of the disease. The earlier results have been reviewed by Kinnicutt, Johnston and Adams. The more recent Muirhead treatment has been reported severally by Rowntree, by Snell and Rowntree and by Rowntree and Snell. These authors reported partial success with the latter method, in that it afforded palliation of symptoms in some cases and prolonged benefit in a few. Similar results were reported by Rogoff with the use of an extract of the adrenal cortex which he called interrenalin and by Goldzieher.

The most dramatic results of specific organotherapy have been obtained with the parenteral or intravenous use of active extracts of the type introduced by Swingle and Pfiffner and by Hartman and his collaborators. The first clinical use of an extract of this type was made in June 1930, when Rowntree and I treated a patient with extract prepared by the method of Swingle and Pfiffner. In January 1931 we reported on a series of 20 patients treated with the preparation of Swingle and Pfiffner. To date, I have had personal experience with the treatment in 34 cases of Addison's disease and, through correspondence, in an additional 7 cases which have not been reported. Search of the literature revealed a total of approximately 200 additional cases of Addison's disease in which preparations of the adrenal cortex were used therapeutically.¹ The results in the entire series agree and confirm the conclusions based on personal experience.

These results indicate that many analogies may be drawn between diabetes mellitus and Addison's disease. As the discovery of insulin was the final step in establishing the rôle of insufficiency of the islands of Langerhans in the pathogenesis of diabetes, the discovery of the cortical hormone has furnished final proof of the rôle of adrenal insuffi-

¹ The articles are listed in the bibliography.

ciency in the pathogenesis of Addison's disease. Diabetes mellitus varies in severity. Cases are recognized in which the cardinal symptoms of diabetes are not shown but the carbohydrate tolerance is reduced—that is, the so-called prediabetic state. Mild diabetes can be controlled by dietary measures alone, but patients with more severe disease do better if they are given insulin in addition. The dose of insulin required is, in part, a measure of the severity of the disease. Insulin, furthermore, is of the greatest value in the treatment of diabetic coma. The treatment of the patient with diabetes and the necessary dose of insulin vary with the stage and severity of the disease. In Addison's disease, likewise, the plan of treatment and the necessary dose of adrenal cortex extract vary with the severity of the disease in each patient. In Addison's disease there is no convenient yardstick, like the sugar content of the blood or urine in diabetes mellitus, with which to measure the degree of the adrenal deficiency, though the necessary dose of adrenal cortex extract is an approximate measure.

Treatment of Crisis. As the most evident results of the therapeutic use of insulin occur in the treatment of diabetic coma, the most dramatic effects of treatment with adrenal cortex extract have been observed in patients in the crisis of acute adrenal insufficiency. The striking clinical changes in patients who respond satisfactorily to treatment are (1) disappearance of anorexia, nausea and vomiting, reappearance of appetite and development of the sense of hunger, (2) relief from fatigue and increase in strength and endurance, (3) disappearance of pain and improvement in sleep, (4) decrease in pigmentation, (5) gain in weight, (6) return of normal gastro-intestinal activity, (7) disappearance of nervous irritability and restlessness and change in the mental attitude to one characterized by hope and euphoria, (8) elevation of the body temperature to a normal level, (9) moderate increase in blood pressure when the patient is in crisis or shock and little change when the patient is in good condition, (10) increased resistance to infection or to the effect of surgical procedure, and (11) partial or complete rehabilitation of the patient, with ability to work.

The most constant and striking effect is the disappearance of anorexia, nausea and vomiting and of the distressing pain in the loins that is present in so many patients with adrenal insufficiency. Increase in strength and endurance appears early and is marked and out of proportion to the objective effects. The decrease in pigmentation may become apparent within three or four days, but there was no change in many patients in the series reported in this paper.

The immediate therapeutic response was satisfactory in the majority of the cases in this series. Variations in the results are inevitable depending on the condition of the patient when he is first seen. In 2 cases the patient was in severe shock at the time of observation and died

before adequate supplies of the extract could be obtained. One patient (case 15) did not respond satisfactorily and died in the hospital, though she was apparently given adequate treatment. This experience at first appears to be in striking contrast to the results of the experiments of Swingle and Pfiffner, who found that adrenalectomized animals, prostrate and about to die of adrenal insufficiency, could be restored to normal health by treatment with adrenal cortex extract. Bilateral adrenalectomy produces acute adrenal insufficiency in an experimental animal with normal reserves of strength and previously unimpaired vitality. The conditions for recovery of the patient with Addison's disease differ from those for the recovery of the adrenalectomized animals, for the patient suffers from a chronic ailment characterized by marked exhaustion and greatly reduced vitality. The recuperative power may be greatly reduced under these conditions, and it is not surprising that treatment may occasionally be without avail. Swingle and Pfiffner have also noted that if treatment is postponed unduly in experimental animals, recovery becomes more difficult. Hartman likewise reported that in the terminal stage of Addison's disease the use of cortical extract sometimes fails to bring about recovery, and he emphasized the development of an irreversible condition. The question of dosage, however, always enters into consideration in such a case, and if the massive doses reported by Kincov, Zillesen and Rowntree could be used more frequently, probably fewer failures would be reported.

Treatment in Cases of Complication with Acute Infection. The susceptibility to infection of the patient with Addison's disease and the importance of infection in the precipitation of a crisis have been emphasized. The slightest sign of infection is a peremptory indication for immediate intensive treatment with adrenal cortex extract. Six patients in this series died as a result of intercurrent infection, usually of the upper respiratory tract. In all these instances, the seriousness of the situation was not appreciated by the patient or his attendants. The initial infection was considered to be mild, and active therapy was postponed until too late. On the other hand, Rowntree, Greene, Swingle and Pfiffner have reported 1 instance (case 10) in which recovery from acute streptococcic sore throat, with bronchopneumonia, resulted from intensive therapy. Similar results were reported by Kenyon in a patient with diphtheria and by Cantor and Scott in a patient with acute bronchitis and subsequent acute cystitis.

Treatment in Cases in Which Operation Is Performed. Patients with Addison's disease are extremely poor risks from the surgical point of view. This condition can be modified by treatment, for several patients in this series had teeth extracted while they were receiving treatment, one patient underwent a minor operation on the nose, and

another, a plastic operation on the eyelid. These minor operations caused no more discomfort or reaction than if the patient had been in normal health—in striking contrast to the severe reaction which frequently characterizes such procedures in cases of Addison's disease in which no treatment is given. An additional case of Addison's disease in association with active tuberculosis of the testis and epididymis was reported by Greene, Walters and Rowntree. Epididymectomy and orchidectomy were done. Adrenal cortex extract was used in the preparation of the patient for operation and was administered as a postoperative measure. The patient made an uneventful recovery, but the tuberculosis was progressive, and two years later excision of the left kidney was successfully undertaken. Snell reported that the patient finally died of miliary tuberculosis.

Treatment in Cases of Partial Adrenal Insufficiency The form of treatment best suited to a patient with Addison's disease who is not in crisis or who has been brought out of a crisis is a highly individual problem and must be determined in each case. Some patients, such as a man (case 14) in the present series, improve markedly while in the hospital and continue to take a small dose of adrenal cortex extract for two or three months after their discharge from the hospital. At the time of writing, the patient just mentioned reported that he had had no treatment since June 1931 and felt well. Roentgenograms showed an area of increased density in the region of the right adrenal, which suggested calcification. Another patient (case 5) likewise reported that she was in good health, though she had had no regular treatment for a similar period. In both these patients the pathologic process in the adrenals apparently was not progressive, and very few signs of adrenal insufficiency were shown. Adenoma-like islands of hypertrophied cortical cells are frequently observed in the adrenal glands in cases of Addison's disease. The functional activity of such regenerated tissue may explain the clinical improvement seen in cases such as the two just mentioned. Unfortunately, a case of this type represents the exception rather than the rule. More commonly, the patient regains a state of relative efficiency, whereby a moderate degree of activity can be maintained, with care and attention to the details of the daily life, a liberal intake of salt and fluids and supportive measures, such as have previously been advised after recovery from the initial crisis. Such patients, however, have little reserve, are readily upset and again pass into crisis. Recovery is possible with early and active treatment, though the initial vigor usually is not regained. Such patients require cortical extract only during the period of crisis, but experience has indicated that recovery is more rapid and complete if treatment is continued for a considerable period after each attack. Further, on the basis of clinical

evidence, the regular administration of small doses of the extract seems to be of value in maintaining the patient's resistance and so preventing the onset of the acute relapse or crisis. In cases of this type the beneficial effects of salt therapy and the use of a diet low in potassium are best seen. The successful management of a case of Addison's disease depends not on the choice of hormonal or of salt therapy but on the combination of the two to secure the best results.

In approximately a third of the cases in which my associates and I have made observations, the pathologic process apparently was active and the course of the illness progressively downward. Temporary improvement can be produced by intensive therapy, but, even at best, the patient's activities are extremely limited, and frequently he is confined to bed. Cantor and Scott reported such a case in which they made observations for twenty-six months, during which period there were fourteen distinct relapses and remissions. Eleven of these were experimentally produced by variations either in the dose or in the potency of the cortical extract which was used in therapy. Similar results were obtained in a patient (case 28) who was studied for a year in connection with clinical tests of different lots of cortical extract. At present, the status of patients who require the daily administration of cortical extract is truly pathetic, for few persons can afford to spend from \$5 to \$15 a day for medicine. In 2 cases in this series the patients deliberately discontinued treatment because of the expense. They died shortly afterward. Seven others were treated for varying periods, but in each case the inability to secure adequate supplies of cortical extract was a factor in the fatal outcome.

The effect of treatment in this series of 34 patients, who have been observed for periods up to six years, is indicated in the table. This table, constructed according to the method of Berkson, shows the total duration of the disease in relation to the percentage of survivors. It indicates that there was an increase in the duration of the disease in the series of treated patients. This increase in the duration of the disease in response to treatment, though slight, is greater than that observed in any other series of cases that has been reported.

The response to treatment is perhaps better shown in the accompanying chart. In this chart the cases are arranged on the basis of the duration of the disease before treatment was undertaken. For comparison with these values, the curve is shown to indicate the percentage of survivors in the series of patients summarized in the table who had no treatment. If the group of patients who were treated is taken as a whole, the duration of the disease before treatment was started corresponds approximately with the total duration of life of patients who received no treatment. In many instances the treatment added little to the apparent life expectancy of the patient. On the other hand 11

of the 34 patients were under treatment for periods longer than the average duration of life of those who were untreated. Four are alive at the time of writing, and all of these persons started treatment more than five years ago. It is probable, therefore, that in a limited group of cases of Addison's disease treatment with salt and with cortical extract definitely increases the life of the patient.

Apart from the effect of treatment in the acute emergencies of Addison's disease and the apparent prolongation of life in selected cases, there are several effects of therapy that may be discussed separately.

Effect on Blood Pressure The effect on blood pressure is slight, as compared with the other changes. When the patient is in shock,

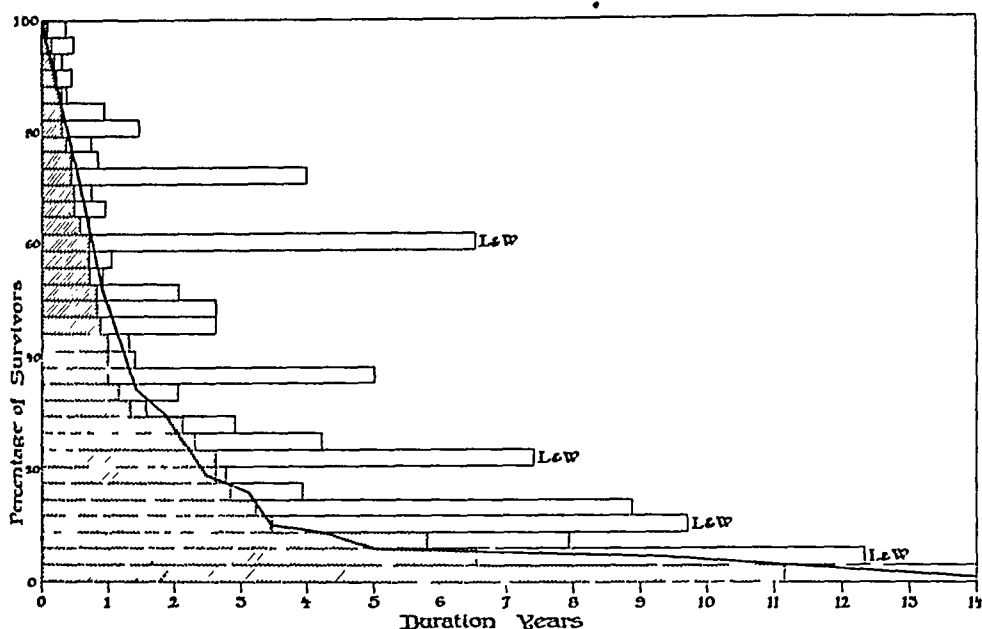


Chart showing the results of treatment in a series of 34 cases of Addison's disease. In this chart the areas of cross-hatching indicate the duration of the disease prior to treatment, and the plain areas, the duration of the illness after treatment. *L & W* means "living and well." One patient (case 22) was living and well in 1934 after being under treatment for four years. She moved away and has not been heard from since, so she is charted as having died at that time. The curve shows the percentage of survivors in a series of 266 cases in which no treatment was given.

the blood pressure may be very low, and, as the shock is effectively combated, the blood pressure rises, *pari passu*, to the lower level of normal. The systolic pressure then varies between 80 and 110 mm. Subsequent increases are slight and apparently are secondary to the general condition and the degree of activity of the patient.

Effect on Pigmentation The degree of pigmentation in Addison's disease bears no direct relation to the severity of the disease, though it has been recognized that in the cases in which pigmentation is the

chief presenting symptom the subsequent clinical course may be slow and the disability slight. In some of the cases a marked decrease in pigmentation is shown after treatment is started. On the other hand, many patients respond well to treatment with adrenal cortex extract, and yet no change in the degree of pigmentation is noted.

Szent-Gyorgyi, in a brilliant series of chemical studies, isolated cevitamic acid from the adrenal cortex. It is now accepted that this substance is identical with vitamin C, the antiscorbutic vitamin. Administration of cevitamic acid is of no benefit to a totally adrenalectomized animal, but Szent-Gyorgyi expressed the belief that the substance plays a rôle in the formation of pigment and stated that its administration causes a decrease in pigmentation in Addison's disease. He therefore recommended a liberal intake of the citrous fruits as part of the diet of patients with this disease.

Effect on Weight. One of the striking effects of the administration of cortical extract is the disappearance of anorexia, nausea and vomiting, the patient again begins to take food, and normal intestinal activity is reestablished. With the taking of food there frequently is gain in weight. One patient gained $9\frac{1}{2}$ pounds (4.3 Kg.) in eight days, and 3 patients, 10 pounds (4.5 Kg.) in one month. Other patients showed no change in weight. In general, one may state that the curve for weight follows the general condition and that gain is a good omen.

Effect on the Gonads. There is much evidence to suggest a physiologic relationship between the adrenal cortex and the gonads. In Addison's disease amenorrhea is a common symptom in women, while men complain of impotence. Several women in this series reported a return of regular menses while they were under treatment, and the men reported an increase in libido and potentia. Similar observations have been made by Hartman, Thompson and Russell, Neumann, Veran and others. Corey and Button reported that the use of adrenal cortex extracts prepared by the method of Swingle and Pfiffner produces precocious sexual maturity in the albino rat, but Levy-Simpson, Kohn-Speyer and Korenchevsky were unable to confirm this observation. Until additional evidence is produced, the changes in sexual function in Addison's disease may be explained on the basis of the poor general condition of the patient, and the benefit derived from treatment may be ascribed to the improvement in the general condition of the patient as well as to specific stimulation of the gonads by the cortical hormone. The cortical hormone has not yet been identified conclusively. At least one of the crystalline fractions isolated from the adrenal gland is related, both chemically and physiologically, to the androgens, but the significance of this relationship is not yet understood. Pregnancy is an infrequent complication in Addison's disease, though Rowntree and Snell recorded 2 instances in their series. Perkins reported that a woman

with Addison's disease became pregnant after treatment with cortical extract was started. She was well during the pregnancy but passed into shock four hours after delivery. Recovery followed intensive therapy with cortical extract.

Effect of Oral Therapy Britton, Flippin and Silvette reported that the oral administration of the cortical extract is effective in prolonging the life of completely adrenalectomized cats, and Grollman and Firor obtained similar results in dogs and rats. The dose, however, was from three to five times the dose required to produce comparable results when given parenterally. The question of expense at present precludes the oral use of cortical extract. On the other hand, the oral administration of dried adrenal cortex or of preparations such as the extracts employed by Rogoff and Stewart, Goldzieher or Hoskins and Freeman is a valuable adjunct to the injection of the cortical extracts. Grollman, Firor and Grollman recently have reported a simple preparation of the adrenal cortex that shows marked activity when administered by mouth. A preparation of proved efficiency such as this should have a wide field of usefulness in clinical medicine.

Effect of Overdosage The clinical picture of tumor of the adrenal cortex is characteristic. This raises the question of possible harmful effects resulting from overdoses of the cortical extract. Toxic effects were occasionally noted after the administration of the extracts first prepared for clinical use. Similar effects have been reported by Benham, Fisher, More and Thuigar, Thompson and Whitehead, Herman, and others. These early reactions were apparently due to the presence of epinephrine or traces of protein in the extract, and they have not been observed with more highly purified preparations. I have seen no symptoms that could be ascribed to overdosage of the cortical extract either in normal persons or in patients with Addison's disease. Kincov, Zillessen and Rowntree gave enormous doses to a patient and reported no untoward reaction. Grollman and Firor likewise could show no effect in animals ascribable to an overdosage.

COMMENT

Numerous attempts have been made to determine the relative rôle of disturbances in the function of the cortical and of the medullary portion of the adrenal glands in producing the symptoms of Addison's disease. Harrop, for instance, suggested that hypotension, hypoglycemia and pigmentation are associated with disturbance of medullary function. Guttman reported that the duration of life is longest in cases in which pigmentation is the outstanding symptom and that cortical atrophy is seen more frequently than tuberculosis of the adrenals in cases of Addison's disease of a duration of five years or more. Guttman, however,

was unable to establish by statistical methods any distinct relationship between the symptomatology of Addison's disease and the type or the degree of involvement of the adrenals. The variability of the symptomatology is perhaps best explained if one considers the chemical compounds which have been isolated from the adrenals and which are supposedly specific products—epinephrine, the lactyl epinephrine of Kendall and his associates and cevitic acid. Finally, extracts containing the so-called cortical hormone have been prepared. Other products may yet be identified. Variations in the clinical picture of adrenal disease may well be explained by variations in the extent to which the production of these substances is disturbed. Recent work has shown that the so-called cortical hormone can be extracted in greater quantity from the whole gland than from the cortical portion, and it is possible that both the medulla and the cortex of the adrenal glands are concerned in the production of this hormone. Final decision is impossible at present, but if the cortical hormone is defined as the substance in the adrenal gland which is essential for maintaining the life of totally adrenalectomized animals, one may state that Addison's disease is due to deficiency in the supply of cortical hormone.

THERAPEUTIC USE OF ADRENAL CORTEX EXTRACT IN CONDITIONS OTHER THAN ADDISON'S DISEASE

Effects in Normal Persons—I observed no definite response to the therapeutic use of adrenal cortex extract in normal persons. Weinstein and Marlow and Norlin and Skoglund confirmed this observation. Hartman, Greene, Bowen and Thorn, on the other hand, reported that in normal subjects injection of 1 cc of extract usually produced some result and that from 3 to 5 cc produced an unquestioned effect which lasted for several hours. Within an hour after the injection the subject was likely to feel sleepy, unless he was engaged in some activity which counteracted this effect. If he went to sleep, he slept soundly for an hour or so. Whether or not a nap was taken the subject felt more active in the evening and seemed to be more alert and physically fit. The sense of well-being was noticeably increased. The night's sleep following the injection of extract of adrenal cortex was more sound, and the subject awoke the next day feeling more rested than usual. This effect on sleep was not observed by a good sleeper but was evident in the light sleeper. When the appetite was faulty, administration of extract of adrenal cortex seemed to stimulate it. Objectively, some subjects showed an increase in the power to do work, as recorded on the ergometer. This increase ranged from 50 to 500 per cent, the high point being reached a few days after the use of the extract was started. There seemed to be an increase in the reserve of energy of any subject

who had been nervous or tired. In 4 of the women the injection of from 3 to 5 cc of extract of adrenal cortex daily for four or five days brought on menstruation from three to five days earlier than usual.

Conditions Associated with Shock—The outstanding features of the clinical picture presented by a completely adrenalectomized dog and by a patient in an Addisonian crisis are characteristic of the shock and anhydiemia which are met in a variety of pathologic conditions in medical and surgical practice. This has led several investigators to conclude that these symptoms are due primarily or secondarily to a deficient supply of the cortical hormone (Zwemer, Harrop and Swingle and his associates). I am acquainted with 1 case of partial intestinal obstruction, with vomiting, dehydration and shock, in which marked improvement resulted from the use of cortical extract. Satisfactory therapeutic response to the use of cortical extracts in the treatment of shock due to acute intestinal intoxication in infants has been reported by MacLean, Sullivan and Zwemer, in cases of shock due to severe burn, by Hartman and by Wilson, Rowley and Gray and in surgical shock, by Rowntree.

Acute Infection—The importance of the cortical hormone in increasing the resistance to infection of the patient with Addison's disease has been stressed. Robbins reported a case in which the condition was diagnosed as acute hypo-adrenalism, occurring as a sequela of acute streptococcal sore throat, and the disease responded to the administration of the extract of adrenal cortex prepared by the method of Hartman, while Hartman reported that the same extract was of value in the treatment of postinfectious asthenia. Neil, likewise, found the extract of value in the treatment of asthenia in a case of chronic bacteremia.

Bamberger and Wendt and Beinhart have reported beneficial results in the circulatory insufficiency of diphtheria. I have seen an apparently specific response in cases of postinfluenzal asthenia. In these different conditions which seemed to respond favorably to the therapeutic use of adrenal cortex extract, exhaustion and muscular or cardiac asthenia were outstanding clinical symptoms.

Results are less sure in various other acute infections. Whitehead and Smith reported the use of cortical extract in the treatment of 1 patient each with typhoid, undulant fever, erysipelas, lymphangitis and sinusitis, with apparent improvement in all instances.

Wenner and Cone reported the use of cortical extract in 28 cases of pyogenic infection of the sinuses of the upper respiratory tract, with improvement in all instances. In these reports the decision with regard to the therapeutic effect of the extract was usually based on the subjective sensations of the patient. Under these conditions, it is difficult to determine the therapeutic effectiveness of a cortical extract.

Operation Involving the Adrenal Gland—Tumor of the adrenal cortex produces a fairly definite clinical picture, and a few cases have been reported in which the tumor was removed successfully. The outcome is not always favorable, for in a considerable number of cases the patient passed into shock after the operation and died, with the clinical picture of acute adrenal insufficiency. These accidents have been explained by the hypothesis that hyperfunction of the tumor tissue produced hypofunction of the remaining normal gland and that normal function was not regained with sufficient rapidity after the operation to prevent the development of acute adrenal insufficiency. I have seen 1 such instance (subsequently reported by Walters, Wilder and Kepler, who have since reported 3 additional cases of this type) in which a diagnosis of hyperadrenalism was made. The surgeon removed a hypertrophied left adrenal gland, and two days after operation the patient passed into shock. Cortical extract was administered for five days, and the rest of the postoperative recovery was uneventful.

Prather also reported a similar case in which the patient passed into shock after the removal of a large hypernephroma and responded well to treatment with extract of the adrenal cortex.

Myasthema Gravis—The response to the administration of adrenal cortex extract was studied in 2 cases of myasthenia gravis. Hartman, Greene, Bowen and Thorn reported 3 cases, and Bernhardt and Levy-Simpson, 8 cases. Improvement was not continued in any of these patients, though Roch, Demole and Duchosal reported benefit in 1 instance.

Muscular Dystrophies—Hartman has treated 6 patients with progressive muscular atrophy and 1 with muscular dystrophy with extract of adrenal cortex. The ultimate course of the disease was not influenced, though there was temporary increase in well-being. Mendelson, on the other hand, reported a case of progressive muscular dystrophy in which improvement with such treatment was marked. I treated a patient with diffuse myositis and profound muscular weakness, but with no benefit.

Disorders of the Thyroid Gland—Possible interrelations between the function of the adrenal glands and that of the thyroid have been discussed at various times. Minnig reported that he obtained brilliant results with extract of adrenal cortex in the treatment of exophthalmic goiter, but he gave no details regarding the types studied or the results obtained. Bram reported similar subjective improvement in 12 cases of exophthalmic goiter in which the oral administration of a glycerin extract of the adrenal cortex was used in treatment. On the other hand, the effect of cortical extract was studied by my associates and me in 4 cases of exophthalmic goiter and by Hartman and his co-workers in a similar number, while Weinstein and Marlow reported 14 cases of exophthalmic goiter and 3 cases of adenoma of

the thyroid with hyperthyroidism. These investigators agreed that while in an occasional case subjective improvement might be shown, the metabolic rate was not affected and that there was no significant change in the clinical conditions.

There was no improvement in a case of myxedema in the present series in which treatment was given or in 2 cases of hypothyroidism reported by Weinstein and Marlow.

Effect on Asthenia—The possible beneficial effect of adrenal cortex extract in various acute infections or of postinfectious asthenia has been discussed. In such cases there is pathologic and experimental evidence of disturbance of the adrenals. There is another group of cases in which at present the condition is variously diagnosed as neurasthenia, psychoneurosis or chronic exhaustion and in which physical and mental asthenia, with great fatigability, gastro-intestinal disturbance and vascular hypotension are marked. No definite pathologic changes in the adrenal glands have been reported in such cases, but functional adrenal insufficiency has been postulated by many clinicians. The cortical extract of Pfiffner and Swingle was used in 8 such cases in this study, but slight improvement was observed in only 1 instance. Hartman apparently obtained better results with his preparation of extract of adrenal cortex, for he reported temporary improvement in 10 of 16 cases studied. Leyton likewise reported marked improvement in suitably selected cases but gave no further details.

Vomiting of Pregnancy—Kemp reported 14 cases of early vomiting of pregnancy in which relief was obtained by the oral administration of dried adrenal cortex. Freeman and Melick reported the injection of cortical extract in a case of pernicious vomiting of pregnancy with relief, while Hartman, Thorn and Potter reported a case of possible adrenal insufficiency, noted during pregnancy, in which there was a response to injections of cortical extract. Stemmer, Herbrand, Anselmino and Torie Blanco likewise reported the cortical extract of great value in treating vomiting or toxemia of pregnancy.

Asthma—Fineman reported on the use of cortical extract in 4 cases of bronchial asthma. In 3 of these an increase in appetite and gain in weight occurred, but marked improvement in the severity of the asthma was observed in only 1 instance. Pottenger was enthusiastic about the beneficial results obtained by oral therapy in 50 cases of bronchial asthma. Cohen and Rudolph gave Rogoff's extract of adrenal cortex to 4 asthmatic patients without effect. The conflicting nature of these reports, the uncertainty regarding the composition and potency of the preparations used and the oral route of administration in most cases make it impossible at the present time to judge of the probable therapeutic value of cortical extract in asthma.

Miscellaneous Conditions—I administered cortical extract in 4 cases of anorexia nervosa, with questionable benefit in 1 instance. Its use has also been tried in individual cases of diabetes, benign hypertension, postural hypotension and erythema nodosum, with no benefit. Questionable improvement was obtained in 1 case each of polyglandular deficiency and generalized tuberculous lymphadenitis. The latter condition, however, was possibly Addison's disease. Kalk reported a case of supposed hypophysial cachexia in which there was no response to pituitary therapy but in which the basal metabolic rate, the appetite and the weight increased after cortical extract was given.

Gruneberg reported improvement in 12 cases of psoriasis and in 1 of rheumatoid arthritis. Josephson reported beneficial effects in glaucoma and in hypertension. Essenson reported similar results in epilepsy and various other conditions. None of these reports were sufficiently detailed to permit the reader to make any objective judgment of the results obtained.

CONCLUSIONS

A series of 34 cases of Addison's disease in which treatment with salt and an extract of the adrenal cortex was used during the period from 1930 to 1937 is reported. The treatment added little to the apparent life expectancy in many cases but definitely prolonged life in a limited group of cases. The duration of the disease was more prolonged in this series of cases than has been reported with earlier methods of treatment.

Clinical experience has indicated that the effect of the administration of extract of the adrenal cortex is specific and limited in effect to Addison's disease or to other conditions in which there is reason to suspect acute adrenal insufficiency. In general, this response has been so specific as to suggest that the therapeutic trial constitutes a reliable diagnostic test, an opinion which was seconded by Geill.

The recorded experience of other observers in general is in agreement. Hartman and his collaborators have reported some benefit in a wider variety of conditions than is indicated in my experience. That adrenal insufficiency in its broadest aspects involves a variety of active principles has already been pointed out. Variations in the composition of various extracts may well explain some of the differing results obtained by their clinical use. The isolation of these principles in pure state by chemists apparently will soon be attained. This leads one to hope that it will not be long before these substances are made available to the physician at reasonable cost. Once this is done there is reason to hope for a better understanding of the rôle of adrenal insufficiency in medicine and of the clinical indications for the therapeutic use of extract of the adrenal cortex.

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INFLUENCE OF GASTRIC ACIDITY AND DEGREE OF ANEMIA ON IRON RETENTION

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We have shown in a previous report¹ that patients with hypochromic anemia retain large amounts of iron when the doses of iron and ammonium citrates are administered by mouth. The results were obtained with the administration of 3 Gm of iron and ammonium citrates per day and were not appreciably influenced by the gastric acidity or the severity of the anemia. The present communication deals more specifically with the effect of these particular factors on the retention of iron when varying amounts of the metal are administered.

It has been shown that iron is absorbed from the duodenum and the upper portion of the jejunum. Lintzel² stated as his belief that it is absorbed only in an ionized form and that an acid reaction is necessary for this ionization, and Verzar,⁴ among others, has expressed a similar view. Mettier and Minot⁵ have shown by means of the reticulocyte response that a better utilization of a small amount of iron is obtained when it is given in an acid medium, but with large amounts a satisfactory response of the bone marrow will ensue, even though the drug is given in an alkaline solution.

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This work was begun in association with Dr C W Baldrige, who died on Nov 22, 1934

1 Fowler, W M, and Barer, A P. I The Retention and Utilization of Orally Administered Iron, *Arch Int Med* **59** 561 (April) 1937

2 Robschuit-Robbins F L. The Regeneration of Hemoglobin and Erythrocytes, *Physiol Rev* **9** 666, 1929. M'Gowan, J P. The Absorption and Excretion of Iron by the Intestines and the Nutritional and Therapeutic Value of Its Salts, *Edinburgh M J* **37** 85, 1930

3 Lintzel, W. Neuere Ergebnisse der Erforschung des Eisenstoffwechsels, *Ergebn d Physiol* **31** 844, 1931

4 Verzar, F, in Bethe, A, von Bergmann, G, Embden, G, and Ellinger, A. *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1929, vol 4, p 72

5 Mettier, S R, and Minot, G R. The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastro-Duodenal Contents in Certain Cases of Anemia, *Am J M Sc* **181** 25, 1931, *J Clin Investigation* **7** 510, 1929

The iron balance of fifteen patients with achlorhydria and eleven with normal or low gastric acidity were studied in an attempt to ascertain the effect of gastric acidity on the retention of iron. All the patients with free hydrochloric acid in the gastric contents, even though it was present only after the administration of histamine, were included in the latter group. The balance studies were preceded by a three day period of adjustment before observations were begun. The balance periods were six days long, and the beginning and end of each was marked by the administration of carmine. The method of study, the technical procedures and the precautions against contamination were given in a previous paper¹

TABLE 1—*Achlorhydria*

Patient	Gastric Acidity	Daily Iron Intake, Mg	Daily Iron Balance, Mg	Hemoglobin, Gm per 100 Cc	Diagnosis
1	0	10.03	-0.71	7.89	Idiopathic hypochromic anemia
2	0	9.13	-10.77	8.10	Hemorrhage
3	0	9.96	-11.05	7.71	Anemia of pregnancy
4	0	10.26	-7.12	12.17	Steatorrhea
5	0	9.72	-7.83	4.58	Idiopathic hypochromic anemia
6	0	11.88	-3.15	5.55	Idiopathic hypochromic anemia
7	0	13.14	+1.24	12.51	Idiopathic hypochromic anemia
8	0	11.89	-9.78	4.78	Idiopathic hypochromic anemia
9	0	11.49	+2.27	7.89	Lead poisoning
10	0	10.17	-4.28	7.45	Hemorrhage
11	0	11.89	+3.01	2.36	Hemorrhage
Average		10.86	-4.379		

TABLE 2—*Normal or Low Gastric Acidity*

Patient	Gastric Acidity	Daily Iron Intake, Mg	Daily Iron Balance, Mg	Hemoglobin, Gm per 100 Cc	Diagnosis
1	Normal	10.12	-2.10	10.20	Hemorrhage
2	Normal	11.96	+2.20	6.23	Hemorrhage
3	Normal	12.51	+1.39	7.45	Hemorrhage
4	Normal	12.27	+2.66	4.07	Idiopathic hypochromic anemia
5	Normal	13.43	-1.19	12.91	Diabetes
6	Normal	9.69	-2.62	10.71	Diabetes
7	Normal	11.81	+3.45	12.62	Arthritis
8	Normal	11.78	+2.64	11.99	Arthritis
9	Low	9.98	-9.91	4.36	Hemorrhage
10	Low	12.57	+2.91	5.65	Idiopathic hypochromic anemia
11	Low	12.25	+1.67	6.66	Idiopathic hypochromic anemia
12	Low	11.96	+4.64	8.45	Idiopathic hypochromic anemia
13	Low	11.78	-1.63	11.78	Diabetes
14	Low	12.87	+6.30	10.81	Diabetes
15	Low	12.85	+4.89	12.05	Diabetes
Average		11.85	+1.02		

The daily intake of iron and the iron balance, the hemoglobin content of the blood in grams per hundred cubic centimeters, and the diagnosis in each case are given in tables 1 and 2. The ingested iron, obtained from food alone, varied from 9.13 to 13.14 mg per day. For the patients with achlorhydria the intake of iron averaged 10.86 mg per day and for those with free hydrochloric acid 11.85 mg. Eight, or 72.8 per cent, of the patients with achlorhydria showed a negative iron balance on this diet, and the average daily iron balance for the group was -4.379 mg. In the group of patients with free hydrochloric acid only five, or 33.3 per cent, showed a negative iron

balance and ten, 66.6 per cent, a positive balance. The average daily iron balance was $+1.02$ mg. This difference between the average daily iron balances for the two groups indicates that achlorhydria diminishes the absorption of dietary iron. This finding is supported by the fact that 72.8 per cent of the patients with achlorhydria showed a negative iron balance, as compared with 33.3 per cent of those having hydrochloric acid in the gastric contents.

If the group of patients with achlorhydria is further subdivided so as to compare the iron balances for those with an idiopathic form of anemia with the balance for those with anemia secondary to a chronic loss of blood, it is found that the average daily iron balance for the five patients with idiopathic hypochromic anemia was -4.04 mg, whereas that for the remaining six patients was -4.65 mg. This variation is too slight to be of significance and demonstrates the fact that there is no appreciable difference in the absorption of iron by the patients with idiopathic anemia and that by those with post-

TABLE 3—Average Daily Iron Balance, Effect of Added Hydrochloric Acid

Patient	Achlorhydria		Hydrochloric Acid Added	
	Daily Iron Intake, Mg	Daily Iron Balance, Mg	Daily Iron Intake, Mg	Daily Iron Balance, Mg
1	14.19	+7.33	12.48	+8.47
2	14.07	+7.12	13.13	+2.48
3	12.67	+2.23	12.79	-5.67
4	11.91	-4.22	12.21	-3.42

hemorrhagic hypochromic anemia when achlorhydria is present in both. We have previously shown that with the administration of large amounts of iron by mouth the patients with idiopathic hypochromic anemia retain and utilize as much iron as do patients with other types of hypochromic anemia. Although faulty iron metabolism has been mentioned as a possible etiologic factor in these cases, our observations do not support this hypothesis.

It has been suggested by previous investigators that the addition of hydrochloric acid increases the absorption and utilization of iron. Table 3 gives the results obtained in four patients for whom the iron balance was studied without additional acid by mouth and again with the addition of hydrochloric acid and pepsin. These patients received 200 cc of tenth-normal solution of hydrochloric acid and 0.5 Gm of pepsin three times daily with their meals. Patients 1 and 2 of this group were not anemic. Neither patient had free hydrochloric acid before the administration of histamine, but both responded to this stimulation by secreting small amounts of acid. Patient 1 retained 7.33 mg of iron and with the addition of acid and pepsin retained 8.47 mg per day. The daily intake of iron in the food was slightly less

during the latter period Patient 2 retained 7.12 mg of iron per day but with the addition of hydrochloric acid retained only 2.48 mg Patient 3, with idiopathic hypochromic anemia and hypochlorhydria, was subjected to the same procedure, and in spite of a slightly increased intake of iron during the period of the administration of acid, the daily iron balance dropped from +2.23 to -5.67 mg Patient 4, with idiopathic hypochromic anemia and achlorhydria, showed only a slight increase with the addition of acid, the daily iron balance increasing from -4.22 to -3.42 mg per day The balance periods in these experiments lasted for twelve days, except for the second period in patient 1, which was only six days These experiments show two patients with a slight increase in the retention of iron after the administration of hydrochloric acid and two with a definitely lowered retention after the same procedure The results are presented as evidence that the addition of hydrochloric acid, even in excess of the usual therapeutic dose, does

TABLE 4—Average Daily Iron Balance (by Periods) with a Daily Intake of 500 Mg, Effect of Added Hydrochloric Acid on Retention of Iron

	Control Period	Period 1	Period 2	Period 3	Period 4
Average daily balance of ten patients presented in previous paper	-4.80	217.93	225.70	202.75	143.49
Average daily balance of three patients with achlorhydria receiving no additional hydrochloric acid	-5.31	238.48	200.24	351.61	386.30
Average daily balance of four patients with achlorhydria but receiving hydrochloric acid	-9.88	189.00	231.73	293.34	200.57

not significantly increase the retention of iron in a patient with achlorhydria receiving a normal dietary intake of iron

Although hydrochloric acid had no significant influence on the retention of iron under these conditions, its effect was studied in patients receiving large amounts of iron Table 4 gives the retention of iron by periods for patients receiving approximately 500 mg of iron per day in the form of iron and ammonium citrates This table includes the average retention of iron in ten patients presented in the preceding paper¹ It is to be noted that the average daily retention of iron in the patients with achlorhydria who did not receive hydrochloric acid was slightly greater, except for the second balance period than the average retention for the entire group When this same group of patients with achlorhydria is compared with a group receiving hydrochloric acid and a similar amount of iron, it is seen that those without the additional acid retained more iron, except in the second balance period than did those receiving acid The differences in the amount of iron retained are not great but are sufficient to indicate that with a large intake of iron achlorhydria does not appreciably diminish the

retention of iron and that the addition of hydrochloric acid does not significantly increase the amount retained

To substantiate further the interpretation placed on the foregoing results, the studies of the iron balance of two patients with achlorhydria who received 3 Gm of iron and ammonium citrates per day are presented in table 5. Patient 1 retained 225.3 mg of iron per day, and with the same intake of iron but with the addition of 60 minims of tenth-normal hydrochloric acid to each dose of iron and ammonium citrates she retained 225.15 mg per day. A second patient had a daily retention of 76.41 mg of iron per day for twelve days, but with the addition of hydrochloric acid only 64.83 mg was retained per day.

TABLE 5—Average Daily Iron Balance with a Daily Intake of 500 Mg

Patient	Iron Balance, Mg		
	During Control Period	During Achlorhydria	With Addition of Hydrochloric Acid
1	-10.77	+225.30	+225.15
2	+17.80	+76.41	+64.83

TABLE 6—Average Daily Iron Balance (by Periods) with a Daily Intake of 500 Mg. Effect of Hemoglobin Content on Retention of Iron

	Control Period	Period 1	Period 2	Period 3	Period 4	Period 5
Average daily balance of ten anemic patients ¹	-4.80	+217.93	+225.70	+202.75	+143.49	+69.13
Average daily balance of five nonanemic control subjects	+2.87	+282.15	+188.31	+243.12	+220.65	+147.12
Average daily balance of five patients with lowest hemoglobin values	-4.94	+174.62	+176.42	+172.99	+82.79	+69.30

It has been stated that an anemic organism leans toward retention of iron,⁶ and animal experiments have demonstrated that a dog rendered progressively more anemic by repeated hemorrhages eliminates smaller and smaller amounts of iron while on a constant intake of iron.⁷ With the depletion of the stores of iron in the body an increased avidity for iron might be anticipated. Table 6 presents data bearing on this question. The average daily retention of iron by five nonanemic subjects was greater during four of the five balance periods than was the average retention of ten anemic persons with the same intake, 500 mg of iron per day. When five nonanemic subjects were compared with

6 Muller, A. H. Die Bedeutung des Eisens bei Anämien. Die Eisenbilanz sekundärer Anämien unter dem Einfluss der Lebereisentherapie, *Ztschr f d ges exper Med* **91** 585, 1933.

7 Fontes, G., and Thivolle, L. Elimination du fer et anémie expérimentale, *Sang* **6** 445, 1932.

the five patients with the lowest hemoglobin content, it was seen that those with a normal hemoglobin value consistently retained more iron. These data are interpreted as indicating that there is no correlation between the hemoglobin level and the absorption of iron when it is administered in large amounts.

A similar conclusion can be drawn from a further consideration of data in table 2. In eight of the patients whose gastric content contained free hydrochloric acid the hemoglobin level was only slightly reduced. The average daily iron balance of these patients on a normal dietary intake of iron was $+1.21$ mg per day, while the balance for seven anemic patients on the same diet was $+0.79$ mg per day. A difference of 0.42 mg per day is not significant, but the trend is in the same direction as that for patients receiving large amounts of iron. Since similar results were obtained under these different circumstances, it seems apparent that a low hemoglobin level does not increase the retention of iron.

Attempts have been made for many years to determine the normal iron requirement of man, and the recent widespread interest in the subject of hypochromic anemia has acted as an added stimulus to this investigation. Reviews of previous experimental work have been given recently.⁸ Lintzel⁹ has stated that a very small amount of iron is required by human beings and that a man weighing 70 Kg can be in iron balance with an intake of 1 mg per day. He stated that if a diet with a constant iron content is given, the body soon establishes a rate of excretion of iron which agrees with the intake and a balance is established. If the diet is increased so as to contain larger amounts of iron, the body again becomes in balance within two days. Farrar and Goldhamer¹⁰ studied four patients who had been receiving a constant amount of iron (from 4.9 to 9.1 mg per day) for periods ranging from forty-one to three hundred and sixteen days and found all the patients to be in equilibrium. The hemoglobin content and the erythrocyte counts were normal at the end of this period, and they concluded that the daily requirement of iron is not more than 5 mg. Ohlson and Daum¹¹ however, in studying three normal women with an average daily intake of 13.78 mg of iron, found the excretion to be 14.95 mg per day, a negative balance of 1.17 mg.

We have determined the iron balance for four women, two with anemia and two with normal hemoglobin and erythrocyte values, during periods of a low and of a normal intake of iron. These diets contained

8 (a) The Iron Requirement of Man, editorial, *J A M A* **105** 1917 (Dec 7) 1935. (b) Farrar, G. E., and Goldhamer, S. M. The Iron Requirement of the Normal Human Adult. *J Nutrition* **10** 241, 1935.

9 Ohlson, M. A., and Daum, K. A Study of the Iron Metabolism of Normal Women, *J Nutrition* **9** 75 1935.

from 3.81 to 6.67 mg of iron per day, although considerable difficulty was encountered in planning a palatable diet of low iron content. It will be seen from table 7 that all the patients on the diet low in iron were in negative iron balance, varying from -1.22 to -5.15 mg per day. Four of these patients were then placed on a diet with a normal iron content, and all of them returned to a positive balance. These balance periods were from twelve to eighteen days long. The consistently negative balance with the diet low in iron suggests that the daily requirement of these subjects was in excess of 5 mg and does not agree with Lintzel's statement that the body adjusts itself to a state of balance after two days of a given intake of iron.

With the consistently negative iron balance in patients on a low intake of iron, it is possible that such diets might lead to a deficiency of iron and to anemia in certain cases, but from the difficulty encountered

TABLE 7—*Effect of Diets with Low and Normal Amounts of Iron on Iron Retention*

Patient	Diet Low in Iron		Diet with Normal Amount of Iron	
	Daily Iron Intake, Mg	Daily Iron Balance, Mg	Daily Iron Intake, Mg	Daily Iron Balance, Mg
1	6.67	-5.15	14.19	$+7.33$
2	6.74	-4.79	14.07	$+7.12$
3	5.99	-2.05	13.14	$+1.24$
4	4.14	-2.90	12.27	$+2.66$
5	5.52	-1.22		

in planning a diet low in iron and from a comparison of this diet with that which had been regularly eaten by our patients with idiopathic hypochromic anemia, we do not feel that it is a frequent cause of such anemia.

COMMENT

These experiments show that patients with achlorhydria retain less iron from a normal dietary intake of iron than do patients with free hydrochloric acid in the gastric contents. This was evidenced by the average iron balance in the two groups as well as by the number of patients in negative balance. It is apparent that this diminished retention of iron may play a part in the etiology in certain cases of idiopathic hypochromic anemia, although we do not believe it to be the only etiologic factor.

Our results show that with a large intake of iron (500 mg per day) the retention of iron is not influenced by the gastric acidity and that the administration of hydrochloric acid, even in large amounts, does not increase the retention of iron. The latter was true both with normal

and with large amounts of iron and indicates that the administration of hydrochloric acid is not necessary for an adequate retention of iron

The previous experimental evidence that an anemic organism has an increased avidity for iron and retains its iron with greater tenacity is none too conclusive, and the results of our experiments on human beings do not substantiate this contention. Nonanemic subjects retained as much iron as did patients with anemia from a normal intake of iron as well as when large amounts of iron were administered. One might expect the reverse to be true when the reserve stores of iron are depleted by chronic hemorrhage, but no evidence of this was obtained.

There is much conflicting evidence in regard to the iron requirement of normal subjects, but recent work has indicated that it is lower than was formerly believed. Fariar and Goldhamer stated their belief that it is not over 5 mg per day. Our results are at considerable variance with theirs, since five patients on a low intake of iron, 3.81 to 6.67 mg per day, were all in negative balance and four of these patients who were placed on a diet with a normal content of iron subsequently showed a positive balance. This indicates that an intake of 6.7 mg per day is not sufficient for the needs of these patients, but as we were not dealing with normal subjects, these results are not strictly comparable to those obtained in healthy subjects.

SUMMARY

Achlorhydria decreases the retention of iron from a normal dietary intake of iron but does not influence the retention when large amounts of iron are administered by mouth.

The addition of hydrochloric acid does not increase the retention of iron with either a high or a normal intake of iron.

The presence of anemia does not influence the amount of iron retained.

A dietary intake of iron of 6.7 mg per day is not sufficient to keep these patients in iron balance.

GENERALIZED XANTHOMA TUBEROSUM WITH XANTHOMATOUS CHANGES IN FRESH SCARS OF AN INTERCURRENT ZOSTER

ADENOCARCINOMA OF THE AMPULLA OF VATER AT NECROPSY

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AND

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PHILADELPHIA

As to the several phases indicated in the title, there is no surprise at the development of xanthomatous characteristics in a zoster lesion since zoster is only one member of the list of diseases the sequelae of which may be fibrous, almost a dozen cases of "scar xanthomas" have already been described in the literature. Nevertheless, this additional illustration of the notorious propensity for xanthomatous infiltration to involve granulation tissue amplifies the knowledge of the conditions under which the infiltration can take place. It is thoroughly established that hypercholesterosis of itself will not guarantee xanthomatous infiltration even in the presence of pathologic fibrous tissue. There are an additional α and perhaps also γ and ϵ factors in the pathogenesis that remain to be sought out. Before one can generalize, one needs more and more data covering both the local and the general conditions under which xanthomas develop in scars, and we feel that our case adds one more item to the accumulation.

As to the association with cancer, this was at the time of its observation almost unique, however, Weidman and Schaffer¹ have recorded another instance—this time in cancer of the stomach—which focuses attention on still another avenue for xanthomatosis and which may perhaps revive interest in the cholesterol-cancer interrelationships. Xanthosarcoma, it is true, is another malignant process involving a joining of xanthomatosis and a malignant process, but here the situation is different, because the two processes are combined in the same cell and do not appear as separate lesions. The carcinomatous phase in our case is especially pertinent because it raises the question of a particular factor,

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1 Weidman, F D, and Schaffer, H W. Xanthoma of the Skin and Larynx, Associated with Carcinoma of the Stomach and Regressive Xanthoma of the Pons, Arch Dermat & Syph **35** 767 (May) 1937

namely, cancer, in the development of the hepatic disease of which xanthoma has long been established as a notorious sequel. The extremely high cholesterol value (1,020 mg per hundred cubic centimeters) is also illuminating, if only from the abstract quantitative standpoint.

If it is admitted that the cancer was the primary factor in the chain of events leading to the xanthoma, this case also shows to what extreme the dermatologist may have to carry his internal medical studies if he would exhaust every possible etiologic possibility in a given case of generalized xanthoma tuberosum.

There is an additional, practical angle to our experience in that an exploratory laparotomy was performed, directed at biliary obstruction, surgery has been drafted but seldom in the therapeutic approach directly to the exciting etiologic factor in a xanthomatous process. The performance of a necropsy on our patient added much to the value of this report, it should stimulate more complete studies of xanthomatous patients in the future.

The prominence of the English in the field of necropsy, even during the era of Virchow, provokes thought as to whether xanthomatous changes are particularly common in England, and, if so, whether English habits of diet and drinking are (or at least were) conducive to this essentially metabolic disease. The creation of the English Xanthoma Committee (Hutchinson, Sangster and Crocker²) points convincingly to the importance of the disease at that time.

REPORT OF A CASE

History—Michael M., a white man aged 44, an ice cream maker, named as his first symptom (August, 1926) a generalized pruritus. Four weeks later, jaundice developed. At this time the stools were of the color of clay, but they promptly returned to yellow.

The xanthomatous nodules developed five months after the onset of the pruritus. They were characteristically distributed on the elbows, knees and rims of the ears and at the angles of the mouth. In contrast to most cases of xanthoma tuberosum, the palms were affected (but without inflammatory areolae as in diabetes), the lesions being concentrated particularly along the deeper creases. Widely scattered lesions occurred on the back, buttocks and extensor surfaces of the arms. At the vertex of the skull there were several large, depressed scars, on roentgen examination the outer plate was found markedly rarefied. The patient claimed that the scars were the result of an old accident, but in view of the presence of certain other scars on the arms and shins, together with a positive Wassermann test of the blood, it was concluded that they were part of an old syphilitic process.

One of the eyes exhibited a large macule of the cornea with irregular refraction throughout the entire cornea. A good view of the fundus could therefore not be obtained. Within eight months the patient lost 35 pounds (15.9 Kg.).

2 Hutchinson, J., Sangster, A., and Crocker, H. Report of Xanthoma Committee, *Tr. Path. Soc. London* **33**: 376, 1882.

The routine detailed physical examination did not disclose abnormalities of the viscera except marked enlargement of the liver (it extended 8 cm below the costal border in the midaxillary line). Accordingly, the gallbladder was drained on three occasions (nine months after the onset of the disease), and from 12 to 16 ounces (354 to 473 cc) of fluid was removed.

The Zoster Lesion—The lesion developed on April 21, 1927, eight months after the onset of the disease, on the left side of the chest along the distribution of the seventh, eighth and ninth thoracic nerves. It was quite characteristic. The xanthomatous changes were observed in it one month later. Some of the papules were red at that time, but on pressure showed a yellowish cast. However, other papules were definitely yellow even without pressure. At this time, a group of minute, punctate yellowish papules was also observed immediately below the lower lip. They had a follicular distribution, i. e., they were uniformly spaced, suggesting that the follicular orifices might have been traumatized as the result of close shaving, and that xanthomatous changes had developed in the microscopic scars which resulted.



Fig 1—Classic location of xanthoma tuberosum on the elbows. The forearms are freckled.

Röntgenologic Examination—The scilla turcica appeared to be normal. The outer plate of the skull at the vertex was rarefied. The gallbladder was not visualized in the twelve or fourteen hour period. The stomach, duodenum, tibia and humerus (metastatic lesions?) were normal.

Laboratory Examinations—Several examinations were made of the urine. The specific gravity ranged between 1.008 and 1.015. A trace of albumin was observed several times, leukocytes and epithelial cells were sparingly found on one or two occasions. There was no sugar.

The feces did not show blood or parasites.

Hematologic Studies—The red blood cells numbered 2,910,000, and the leukocytes, 16,200 and 19,000. The hemoglobin measured 9.7 Gm.

Blood Chemistry—The dextrose measured 100 mg, and the urea, 11 mg, per hundred cubic centimeters. The van den Bergh reaction was positive on the

immediate test, the icteric index was 45. The coagulation time was four and a half minutes, the bleeding time, two and a half minutes. The Wassermann test of the blood was at first positive, but later negative. The blood cholesterol measured 960 and 1,020 mg per hundred cubic centimeters on two different occasions, yet the serum was not milky.

Electrocardiographic study gave a normal tracing.

Biopsies were performed three times (May 7, Aug 30 and Nov 28, 1927), twice at an earlier stage of the xanthomatosis and once later, after the zoster had developed. In the first specimen examined, classic xanthoma cells appeared, they were confined to the uppermost parts of the corium, crowding the papillae, abutting directly on the basement membrane above and extending around blood vessels in the subpapillary region and slightly deeper. There were no giant cells.

In the second specimen taken for biopsy (from the elbow), the processes were found to be regressive, i. e., the epiderm had become denuded, probably as the



Fig 2—Linear distribution of xanthomas on the palms, inflammatory areola such as occurs in diabetic xanthoma was absent.

result of traumatism, and the foamy quality of the cytoplasm could be only vaguely recognized. The xanthomatous areas appeared as an indifferent pink granular matrix, interspersed with distorted spindle cells. Evidently the nuclei of the xanthoma cells, although once compromised as to vitality, were returning to an approximately normal state. If this is true, in so doing they indicated their original nature, i. e., they were spindle cells rather than cells of the reticulo-endothelial system.

At the third biopsy both an older lesion from the elbow and a recent one from the healed zoster (now xanthic) were examined. The observations on both the lesions were the same as those of the first biopsy, except for a notable polymorphonuclear infiltration around the hair follicles in the zoster lesion. This should not be referred to unabsorbed infiltrate from the zoster, because the patient also had an abscess of the lobe of the ear at this time, and had, in fact, complained a number of times about the development of pustules in xanthomas elsewhere—on

the fingers, for example. Singularly, only the xanthoma cells in the subpapillary regions stained with sudan III in frozen sections, deeper ones did not take the dye. Crystalline forms (rods) and cholesterol crystals were not recognizable. It should be remembered that the zoster lesion was a comparatively acute example of xanthomatous change (seven months' duration).

Pus from the ear, stained by Giemsa's stain, showed that nearly all of the leukocytes were eosinophils. There were many intracellular diplococci.

As fats in subcutaneous tissue had been successfully stained with carotene,³ this substance was tested on frozen sections of xanthoma lesions. In no case did the fat become colored until sections had been heated. Thereupon, the fat globules coalesced, it was then possible to make out a faint yellow coloration in the larger globules but not in the smaller ones.



Fig. 3—Xanthomas in zosteriform distribution

Clinical Diagnosis —The clinical diagnosis was xanthoma tuberosum multiplex, hypertrophic biliary cirrhosis of the liver, malignant degeneration, herpes zoster and syphilis.

Exploratory Laparotomy—Nineteen months after the onset of the disease, exploratory laparotomy was performed, directed toward possible biliary obstruction. It was recognized that the cystic duct was enlarged to the size of an average thumb, and that the head of the pancreas was indurated, however, biliary obstruction could not be demonstrated. Small deposits in the wall of the large and small bowel were considered to be deposits of cholesterol. The patient died on the operating table from cardiac failure.

³ Weidman, F. D. Carotin as a Specific Fat Stain, as Demonstrated in Frozen Sections, Proc. Path. Soc. Philadelphia, 1927, p. 24.

Necropsy.—Necropsy was performed forty-eight hours after death. All of the organs and tissues were deeply jaundiced. The gallbladder exhibited a mild chronic inflammation, it was thick walled and small, and had collapsed. It contained no stones, but its lining was deep red and incrustated by bile-stained, chalky material. The bile was pale, intermixed with about 5 cc of a deep green amorphous substance. All of the bile ducts were definitely dilated, had thickened fibrous walls and were lined by bright yellow granular incrustative material. There was definite narrowing at the papilla of Vater, however, it was possible to pass a probe into the biliary passages. The common duct immediately above the papilla

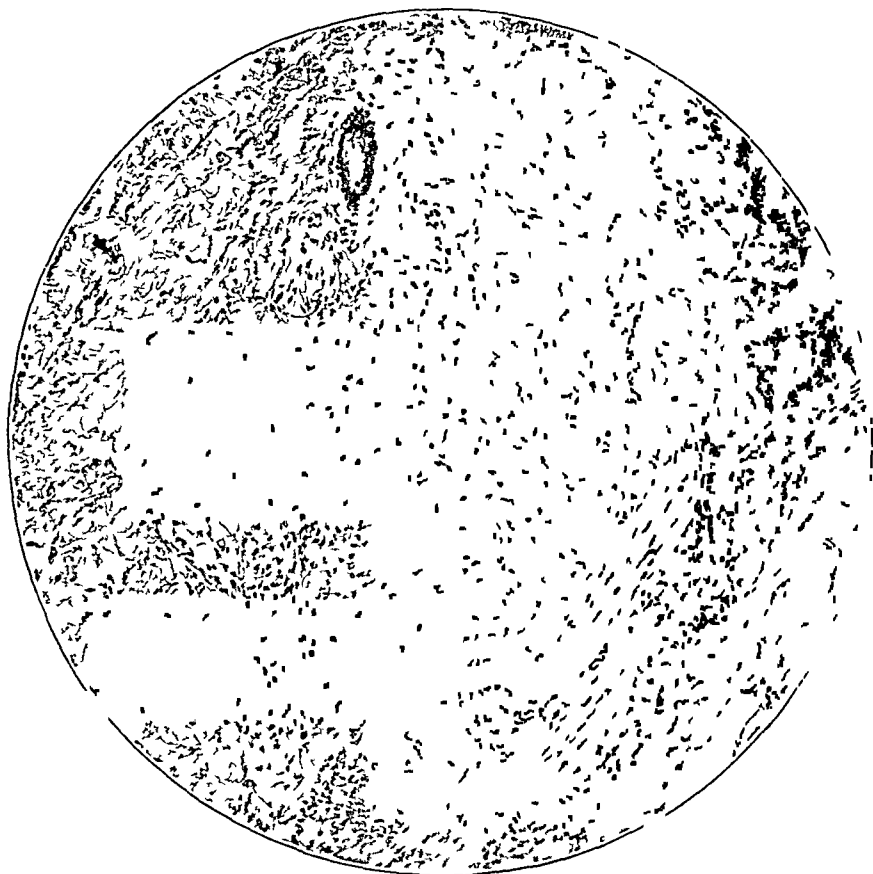


Fig 4—Focus of xanthoma cells in relation to pilosebaceous apparatus (biopsy specimen taken from the skin)

of Vater was particularly dilated (3.5 cm in circumference). Formation of tumor could not be demonstrated, the indurative processes were regarded as being chronic inflammatory.

The liver was enlarged, weighing 2,820 Gm. It was deeply jaundiced, but had a much more smooth surface than was expected. Otherwise, it had the characteristics of biliary cirrhosis. The linings of the intrahepatic bile ducts were encrusted with bile-stained chalky material similar to that encountered in the gallbladder.

The kidneys were enlarged, weighing 200 Gm each. The conspicuous feature in them was the yellow streaking in the pyramids, reminding one of the streaks of uric acid in gout.

The adrenal glands were small. They had an extremely narrow cortex, and the yellow lipoidal substance was present only in restricted parts.

There were one or two plaques of bright yellow atheroma on the lining of the left auricle. The valves were comparatively normal, there were no signs of syphilis anatomically in either the heart or the aorta. The aorta showed, likewise, a few plaques of atheroma, some with hyaline changes in addition. The changes were not, however, of syphilitic type. It is emphasized that, besides a very early atheroma, there were separate and distinct brighter yellow deposits scattered through the entire length of the aorta. The same was true of the pulmonary arteries.

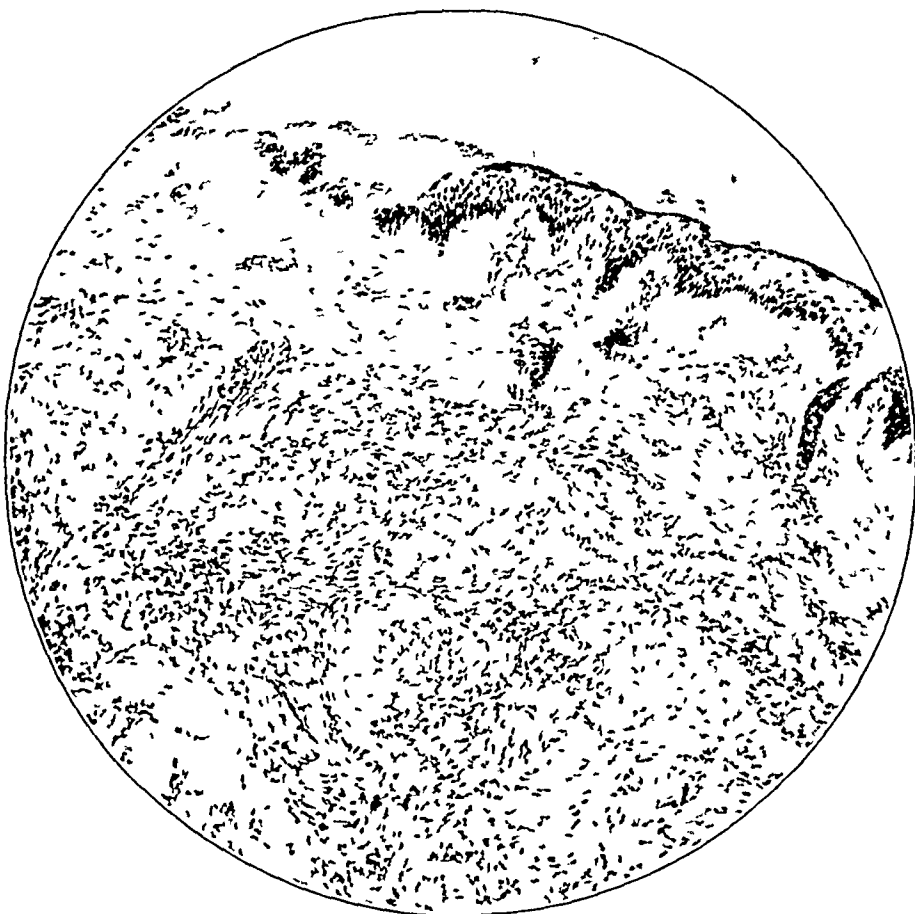


Fig 5—Regressive lesion on the elbow. Only spindle cells remain, there are no xanthoma cells. The epiderm over this very old lesion was largely destroyed by traumatism.

The spleen was large and covered with hyaline plaques. In addition, there were numerous thin flat bright yellow deposits on the capsule.

The pancreas was somewhat hard, but otherwise normal.

The esophagus, stomach and large and small intestines appeared normal except for an occasional yellowish patch in the intestinal wall, such as the surgeons had recognized at operation.

All of the internal lymph nodes were definitely enlarged, averaging 1 cm in diameter. They were soft and edematous, and many of them showed small bright yellow areas similar to those found on other organs.

The testicles, epididymis, seminal vesicles, prostate and prostatic urethra appeared normal.

The thyroid gland appeared normal

The peripheral arteries were mildly atheromatous

The brain was of such soft consistency that its substance had a tendency to fall away (the autopsy was performed forty-eight hours after death) The dentate nuclei were severely sclerotic

Gross Anatomic Diagnosis—The heart showed slight hypertrophy, cloudy swelling and jaundice There were deposits of cholesterol in the endocardium The left lung showed partial collapse of the lower lobe There was slight congestion of both lobes The right lung showed congestion and jaundice The spleen presented diffuse hyperplasia and deposits of cholesterol in the subcapsular tissue

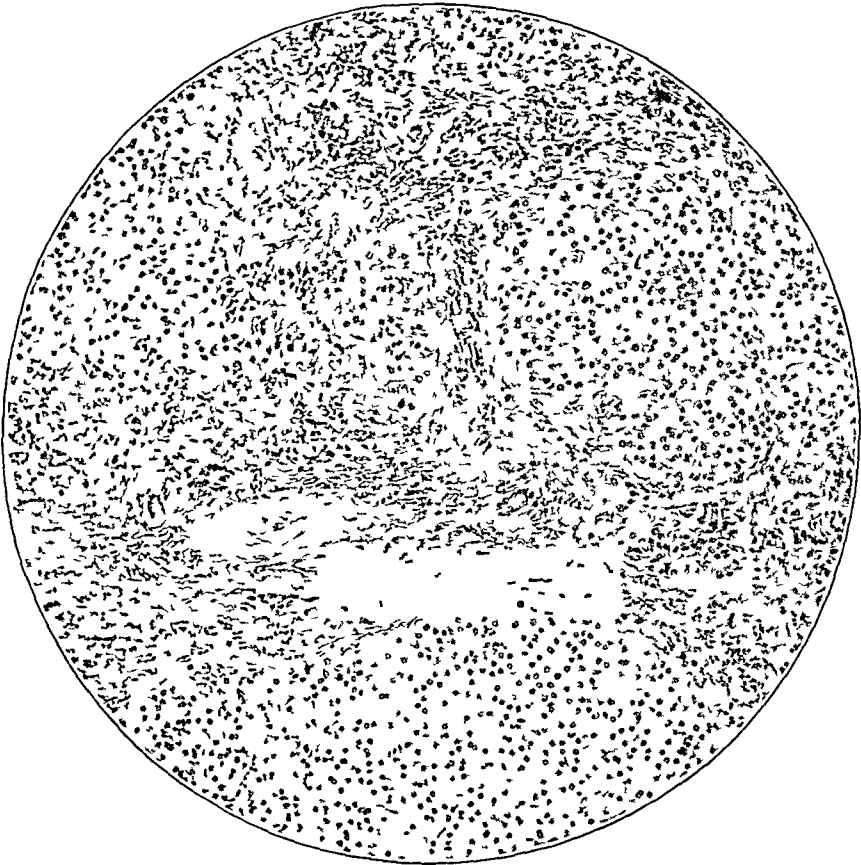


Fig 6—Hypertrophic biliary cirrhosis of the liver Parenchymal cells do not exhibit cramming of cholesterol

The kidneys were jaundiced and showed old infarcts, cloudy swelling and deposits of cholesterol in the pyramids (?) The liver showed hypertrophic biliary cirrhosis The biliary system showed dilatation of all ducts with deposits of cholesterol in the mucosa There was chronic inflammation of the papilla of Vater There were deposits of cholesterol in the intima of the aorta The lymphatic system showed hyperplasia and deposits of cholesterol (?) The brain showed marked general edema, with congestion There was severe sclerosis of the dentate nucleus

Histologic Examination—In addition to sections embedded in paraffin and stained by hematoxylin and eosin, frozen sections stained with sudan III were made

from the liver, kidney, adrenal glands, spleen and aorta, i e., the organs which were expected to show fatty changes

The lungs showed no evidence of xanthomatous change or metastatic cancer. Areas of collapse and fibrosis, with small foci of calcification of the bronchial cartilages, comprised the pathologic features.

The muscle fibers of the heart were narrow and coarsely granular, the transverse markings were invisible. There were no xanthomatous changes.

Sections of the liver stained with hematoxylin and eosin confirmed the gross diagnosis of a high (but not extreme) grade of biliary (not Hanot's) cirrhosis. Bile ducts and fibrous tissue of Glisson's capsule were moderately hyperplastic, and

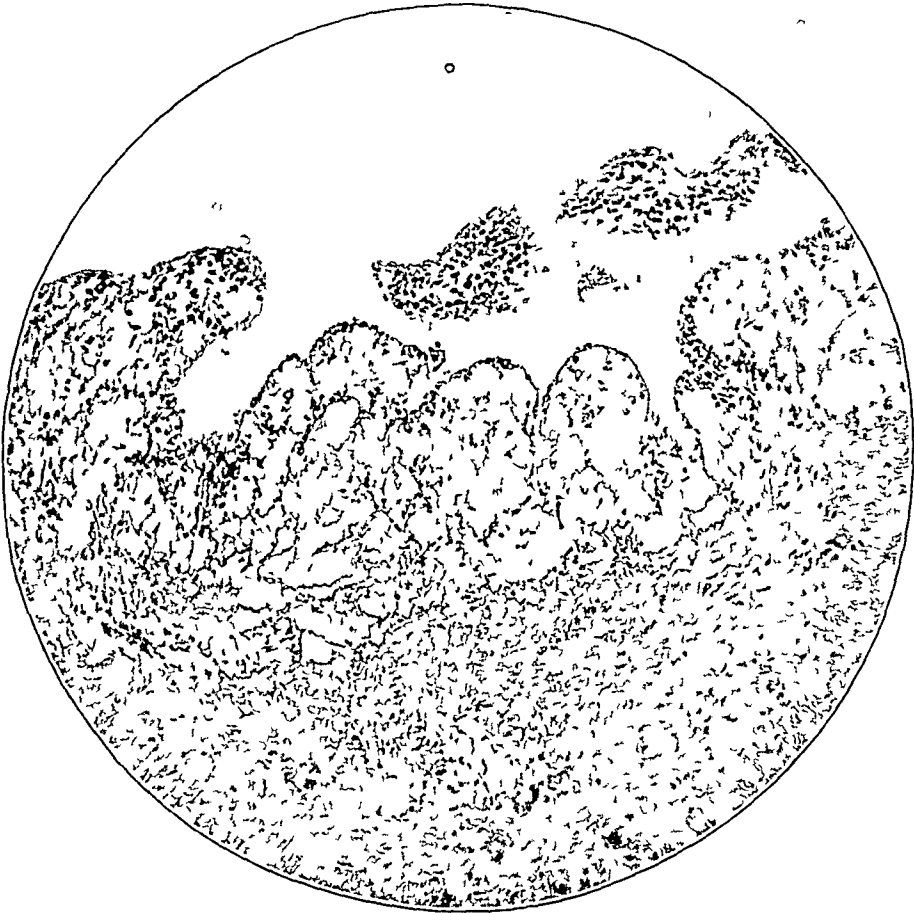


Fig 7—The wall of the gallbladder, the spongy network has probably come about through a fusion of the xanthoma cells

there were much bile pigment and numerous polymorphonuclears in the latter. The parenchymal cells were small, the Kupffer cells were broadened by bile pigment and indefinitely outlined vacuoles. The picture was not suggestive of cranning of cholesterol. In frozen sections stained by sudan III the parenchymal cells were crowded with fine pigment granules, and at times with other granules which stained yellowish, as with a poor sudan III stain. It is surmised that these represented combinations of protein and fatty substances. In the Kupffer cells, however, deep red-staining globules (neutral fat) were seen in abundance. No crystals were found until a few widely distributed, doubly refracting ones were brought out under the polarizing microscope. Such crystals appeared always in the interstitial substance.

The wall of the gallbladder was only slightly thickened, in paraffin sections it measured 3 mm in thickness. The mucous membrane was not recognizable, the lining consisted of a delicate membrane, evidently the basement membrane of the mucosa. The fibrous tissue immediately underlying the latter was coarsely reticular, apparently the tissue interstices had been tremendously overdilated, probably by lipoids. The resultant spaces were much larger than xanthoma cells and most irregular in form, they intercommunicated and contained moderate quantities of coarse pink granules. Moderate numbers of lymphoid and plasma cells (polymorphonuclears were absent) were located on the reticulum, whereas larger numbers occurred from place to place immediately under the basement membrane.

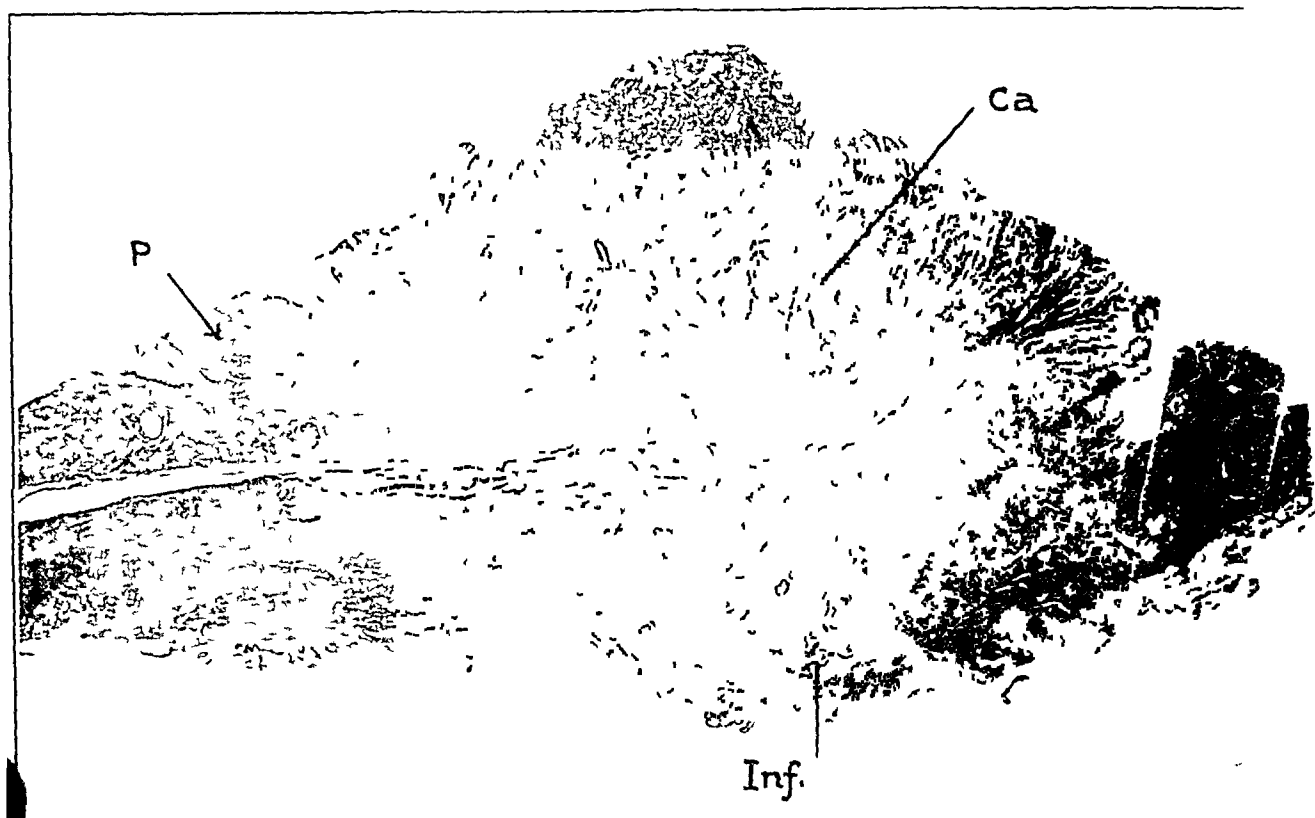


Fig 8—Adenocarcinoma of a duodenal papilla. Mucosa of the common bile duct is shown below, that of the duodenum, at the top. The pancreas is indicated by *P*, the cancer, by *Ca*, parts infiltrated by cancer tissue, by *Inf*.

The capillaries in this region were highly congested. The same order of changes occurred focally from place to place in other locations, even in deeper parts of the muscularis, but far less intensely. Thus, the spaces occurred individually or as loosely connected, comparatively widely separated groups of spaces, that is, they were unlike xanthoma cells. The general effect given was that of a thin plaque of lipoidal infiltration located immediately under the mucous membrane, with scantier extensions into the muscularis. The glands appeared to be normal in number, but their lining cells were moderately hyperplastic and had large nuclei rich in chromatin. It did not appear that the acini had proliferated. The muscular tissue no longer appeared as such, it was represented by pink granular compara-

tively anuclear material disposed in strands between hyperplastic fibrous tissue bundles

The mucosa of the common bile duct was recognizable on one side of the section by its plications, practically all of the epithelial covering had disappeared, as in the case of the gallbladder, leaving only the basement membrane as the surface covering (autolysis?) In general, the changes here were the same as those described for the gallbladder, including the lipoidally distended spaces, glands and infiltrate of round cells. The glands, however, were definitely hyperplastic and took on adenomatous configurations. They were so close to the focus of carcinoma which appeared on the intestinal side of the section that they were intermixed with plugs



Fig 9—Infiltration of muscular tunics by adenocarcinoma at the duodenal papilla

of cancer cells which had obviously extended from it by direct metastasis. We do not believe that these glands were participating in the malignant phases of the situation. Indeed, at one place cancer cells were located immediately under the basement membrane.

The opposite side of the section permitted the recognition of intestinal mucosa. Irregular columns of disorderly hyperplastic cells extended perpendicularly from the surface with intervening partitions of involuntary muscle. The cells were in part simple and columnar, but in the deepest position exhibited metaplasia into rounded, polygonal or seal-ring forms. Not infrequently they occurred in strips or even as atypical tubules. The rounded and polygonal forms were found infil-

trating the deepest parts of the muscularis and extending even as far as the mucosa of the bile duct. Even in these advanced positions the conformation of some of the cell groups was acinar. Cytologically, the characteristics common to cancer cells were satisfied, such as the large size of the cell cytoplasm and the nucleus, the abundance of chromatin and the mitotic figures. Xanthomatous changes could not be recognized with certainty in any of the cancer cells. Portions of autolytic pancreas were included in this section, the most peripheral portion of the cancer infiltrated it, but it was clear that the pancreas itself was not participating in the malignant hyperplasia.

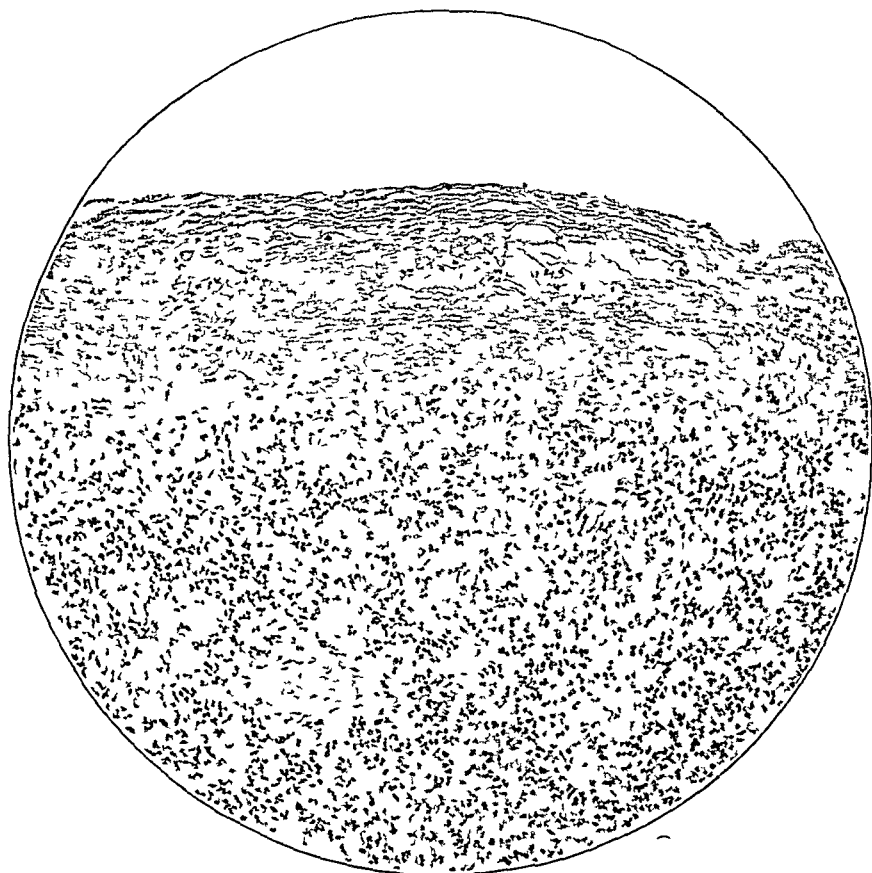


Fig 10—Xanthoma cells in the capsule of the spleen

Moderate xanthomatosis of the muscle cells in the external tunica muscularis was the only explanation of the yellow streaks reported in the intestines at operation and necropsy.

The capsule of the spleen was of normal thickness, in several places it exhibited reticulated foci suggestive of gigantic, fused xanthoma cells. The outlines of the latter could not be made out, but the granular substance in the spaces contained small pyknotic nuclei which in a way resembled arterial atheroma. The reticular parts of the stroma were markedly thickened, but almost bare of lymphoid cells. There was no hyperplasia of the endothelium. Isolated xanthoma cells were identified in the pulp, but only after careful search. The splenic nodules were small but rich in lymphoid cells. The erythrocytes in the sinusoids appeared autolytic, blood pigment was normal in quantity.

In the paraffin sections of the adrenal glands the only abnormality consisted in the extreme scarcity of lipoidal globules in the pars fascicularis, cytoplasm were coarsely granular in all parts of the cortex. In the frozen sections, all cells except those of the pars glomerulosa contained large numbers of small deep red-staining globules. In many areas, however, masses of large globules also occurred, but there were no crystals. The observations as to doubly refractile crystals were the same as those in the liver, i. e., there were only widely scattered, isolated crystals, even among the masses of deep red-staining neutral fat globules.

The paraffin sections of the kidney were not particularly informative, the positions occupied by the crystals in the pyramids could indicate edema morpho-

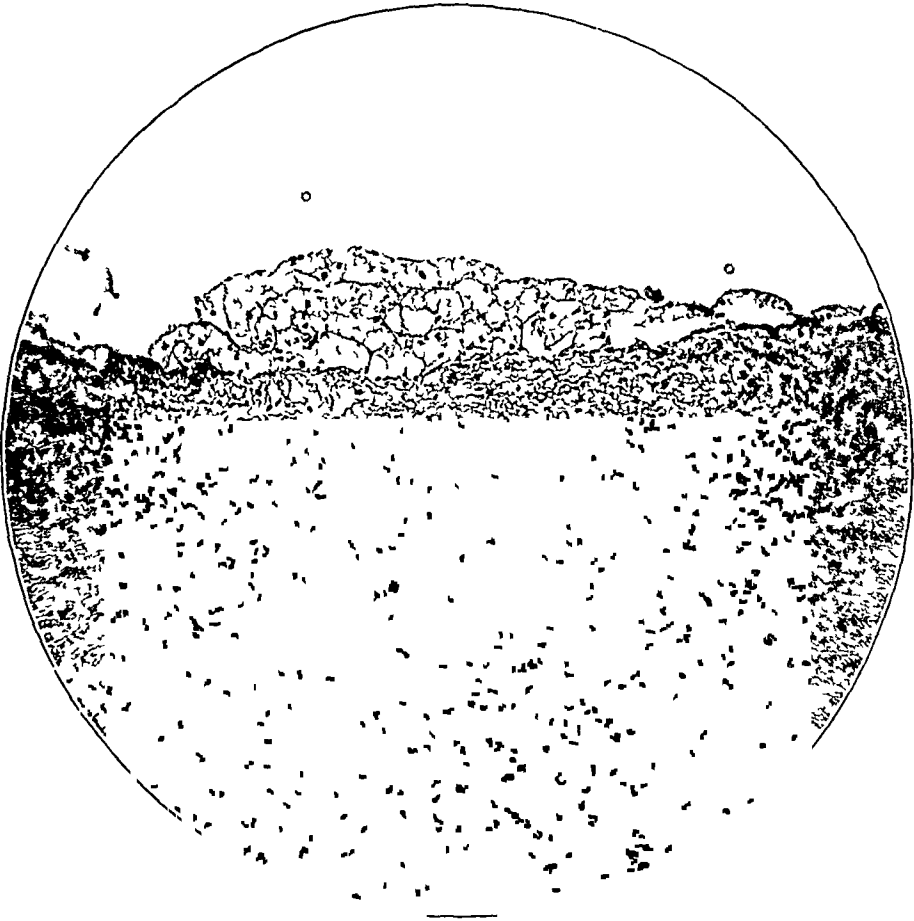


Fig. 11—Intimal xanthomatosis, formation of xanthoma cells in the hyperplastic endothelium of the aorta. The pulmonary artery and the mural endocardium also exhibited this type of change.

logically as readily as they could lipid content. The cytoplasm of the parenchymal cells appeared normal, cramming by cholesterol was not indicated morphologically. In addition to the abundance of bile pigment, which was to be expected, there were a few rather large masses of short, needle-shaped crystals in the frozen sections which had a greenish cast and which lay in the interstitial substance and not in the lumens of the tubules, as had been expected from gross observation. The crystals were doubtless the basis of the yellow striae that were commented on previously. With sudan III the crystals stained deeply red, whereas the bile pigment took an indifferent yellowish red color, something like that given by poor staining. Under

the polarizing microscope, only small numbers of the needle-shaped crystals were doubly refractive

Short stretches of xanthoma cells lay on the intima (infiltrated endothelium) of the aorta with features readily distinguishable from those of atheroma, i. e., they had sharp outlines, did not fuse and had a distinctive piled-up appearance on the lining. In addition, poorly outlined clusters (foam cells) were discoverable in the media, these could not be distinguished from the foamy cells of atheroma. In frozen sections, great numbers of small deep red-staining crystal-like rods were found scattered throughout the intima both singly and in masses. In addition there were other rods of the same size and shape, which did not stain red. Very few of the crystals were anisotropic, as in the case of the liver, spleen and other organs, it was possible to identify them only at wide intervals. Although most of them lay in the intima, a few could be found also in the media.

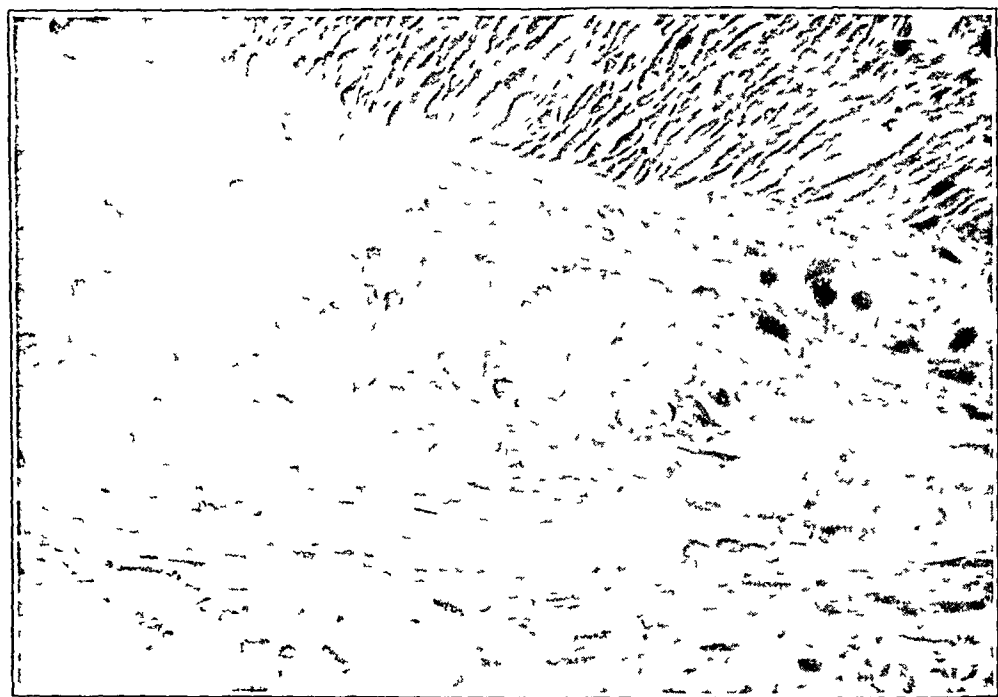


Fig. 12—Beginning of foaminess in the cytoplasm of the smooth muscle cells of the intestinal wall. This focus is selected to demonstrate that it is the muscle cell and not the fibrous tissue that is concerned. Areolar subperitoneal tissue is visible at the bottom of the photograph.

Extreme grades of endarteritis nodosa were observed in most of the arteries examined, but there was no atheroma.

Paraffin sections of the skin reproduced the conventional picture of xanthoma tuberosum. The classic foam cells were distributed in groups or masses at all levels of the corium, but they still had a predilection for the upper strata, occurring even in contact with the basement membrane of the epiderm. They showed a tendency to be concentrated in certain more or less perpendicular tracts aligned with the peripheries of hair follicles. This arrangement could be referred to concentration of the xanthoma cells in the larger lymphatic spaces which are known to surround such structures as hair follicles and blood vessels. A few of the xanthoma cells were multinucleated or so-called giant xanthoma cells. Cholesterol clefts were not seen.

As to the kinds of lipid in the skin of this patient, as revealed in a frozen section, by all odds the predominant one was neutral fat, which stained intensely red with sudan III. With the polarizing microscope it was possible to make out that there were also goodly quantities of doubly refracting lipoids in a more or less crystalline form. There were much larger masses of the latter in the skin than in the other organs which we have described and which were examined by this technic. We estimate that fully 50 per cent of the fatty substance in the skin consisted of doubly refractile substance (cholesterol?), and that the remaining 50 per cent was not doubly refractive (neutral fats and fatty acids).

Spindle cells were uniformly swollen throughout the section and loaded with large, red globules of neutral fat. Incidentally, the epiderm participated in the fatty change, as has been described by other authors, red globules were abundantly present in the basal cells. Furthermore, fat globules such as Pautrier⁴ pictured, which he referred to as part of a purposeful transfer of particulate matter from the corium into the epiderm, were observable in spindle cells immediately below the basement membrane.

The mucosa of the urinary bladder was autolytic. The rest of the wall appeared normal.

Xanthomatous changes were not recognized in the pancreas. The only abnormality consisted in a moderate interlobular fibrosis.

Histologic Summary. First and foremost, a neoplasm was established as the cause of the biliary obstruction, it was primary in the mucosa of the bile duct. The gross diagnosis of biliary cirrhosis (not Harot's) was confirmed.

All doubt was removed as to the nature of the yellow deposits in the splenic and hepatic capsules and on the mucosa of the gallbladder and the aortic lining, they were xanthomas and not simple atheromas or fatty degenerations.

Carcinomatous metastasis was not disclosed in any organ, nor were xanthoma cells observed extensively within the parenchymatous cells of an organ, there were only isolated xanthoma cells in the spleen and liver, which are the commoner depots for storage of cholesterol. That is, there was no evidence of surplus cholesterol, morphologically, except in the skin.

As to the particular kinds of fat indicated, in none of the viscera examined was it possible to find more than a few widely scattered short needles, which were anisotropic and which could be interpreted as cholesterol. There were great numbers of needle-shaped crystals of the same form as these, but they stained a deep red and were not doubly refractive. The inference is that the fatty substances in our case, at least by the time they reached the microscope, were in the form of neutral fat rather than cholesterol.

It should be added that the same changes were observed in frozen sections in two different lots of material. The first lot had been kept frozen for six days. The second lot had been promptly fixed in formaldehyde at necropsy, although the organs had been preserved for two days before sectioning. It is necessary to record such conditions in view of the known propensities for the fatty substances in xanthoma to undergo morphologic changes when preserved for some time in formaldehyde.

In view of the indefiniteness of xanthoma cells which so often obtains because of their vague boundaries, the situation in the wall of the gallbladder merits atten-

4 Pautrier, L. M. Dermo-Epidermic Interchanges as Controlled by Study of Melanic Pigment, Esters of Cholesterol (Xanthoma) and Hemosiderin (Schaumburg's Disease), *Arch. Dermat. & Syph.* **17**: 1 (Jan.) 1928.

tion Thus, the lipid substances in the submucosal plaques lay free in tissue spaces, not in xanthoma cells It was, in effect, a lipid edema, such as Bross⁵ also noted

PATHOGENESIS

Beginning with the hepatic disease, whether syphilis or carcinoma was the primary exciting factor, there resulted a high grade of hepatic damage, admittedly an outstanding cause of hypercholesteremia and consequent hyperlipoidosis Thereafter, the genesis of the cutaneous lesions becomes understandable, in the presence of actively growing and actively dividing fibrous tissue cells, the excess fat entered the cell and was retained there, with the result that xanthoma cells were produced We are unable to state what the incentive was to young fibrous hyperplasia in our patient, but the multiple abscesses were consistent developments on the skin and were perhaps secondary to the infection of the biliary tract Evidently the old scars on this patient, such as the normal one at the umbilicus, that at the site of antismallpox vaccination and the syphilitic scars of the scalp and arms, were not in the appropriate biologic phase to accept and retain the substances

Cause of the Hepatic Disease—In our case, the conclusion as to which was the primary lesion in the disease complex—cancer or syphilis—is contingent entirely on the age of the lesion at the duodenal papilla From the clinical history it appears that the disease began nineteen months before death supervened The carcinoma was exceedingly small, it could not be delineated grossly, but was not more than from 8 to 10 mm in diameter, as judged in histologic sections It seems impossible to conclude finally that such a small carcinoma could be nineteen months old or, on the other hand, that it was of only recent development, one can only speculate The features were not quite those of adenoma malignum, which is a form of carcinoma conceded to be very slow in growth The carcinoma was definitely infiltrative However, the absence of metastases in regional lymph nodes speaks for the comparative benignancy of this particular cancer Adenomatous hyperplasias with minute polypoid formations frequently occur at the biliary outlet (Dardinski⁶), and may well have preceded the adenocarcinoma in our case

On the other hand, it is possible to construct another hypothesis, such as that of an initial syphilitic hepatitis masked by the subsequently developing biliary obstruction, the mildness of the fibrosis of the liver could be invoked in support of this idea This would imply that the hepatic damage antedated a biliary obstruction, but to us this line of thought

5 Bross, K Generalized Xanthomatosis, *Virchows Arch f path Anat* 227 145, 1920

6 Dardinski, V J Inflammatory Adenomatoid Hyperplasia of the Major Duodenal Papilla in Man *Am J Path* 7 519 (Sept) 1931

would lead to such interminable speculation as to the relative susceptibility of the liver and the wall of the gallbladder to irritants and as to various other involved considerations that this hypothesis cannot be fertile of results

As to syphilis in the case, the serologic reports were conflicting, the Wassermann reaction of the blood was positive at the first examination and negative at the second. Much more important were the scars of the scalp and arms—favorite sites for syphilis. On the other hand, the aorta did not show the syphilitic type of arteritis at necropsy. We feel, however, that in this patient the balance of evidence decidedly favors syphilis, the cutaneous lesions turning the scales.

Our first impulse was to favor the hypothesis that there was an initial syphilitic cirrhosis accompanied by hypercholesteremia, and that the carcinoma finally became intercurrent. The obstruction thereupon added a biliary type of cirrhosis which masked the antecedent syphilitic cirrhosis. We were influenced somewhat toward this opinion because we had recently witnessed at necropsy a carcinoma of the stomach which was associated with a regressed xanthoma of the pons and xanthoma tuberosum of the skin¹. It seemed more than a coincidence that two malignant tumors should be encountered in two consecutive cases of generalized xanthomatosis under the observation of the same physicians, particularly since necropsies in cases of generalized xanthomatosis are exceptionally rare.

At this point, the case of Kriebich⁷ applies. Syphilis was likewise present in his patient, but at such an early stage (nine months) that cirrhosis at least could not have been a factor, although there was still a remote possibility that the arsenical therapy which the patient had received had played a part and caused hepatic damage. The welcome contribution to the immediate problem is Kriebich's citation of gastric crises as the occasion for a zoster, as in our patient, at least, similar neurologic considerations are involved. This item probably carries more weight than any other chronological evidence in our case, i. e., as to the duration of the lesion of the duodenal papilla. If one may assume that a lesion of the duodenal papilla inaugurated the zoster, it would establish itself rather than syphilis and hepatic damage as the initial factor in the entire disease complex, because it will be recalled that the zoster made its appearance only four months after the initial pruritus and three months after the onset of jaundice.

All things considered, we feel that an adenomatous polyp at the duodenal papilla was the beginning of the entire disease complex, and that the cancer developed secondarily on the polyp at a comparatively late date.

⁷ Kriebich, C. Zosteriform Xanthoma, *Arch. f. Dermat. u. Syph.* **152** 365 (Dec. 3) 1926.

INTERNAL XANTHOMATOSIS IN GENERAL

It is seldom that xanthomatous infiltrations have been demonstrated in internal organs in xanthoma tuberosum, largely because necropsies have been so rarely performed. The table which follows contains all the references we could find. Even in Pinkus and Pick's⁸ case, although a necropsy and exhaustive studies were made, little was added to the knowledge of the internal distribution of xanthoma. In our case, the presence of the deposits in the capsules of the liver and the spleen, in the aortic intima and in the walls of the intestines connoted an association with endothelium (serous surfaces) which was consistent with the habits of xanthomatous infiltrations in general and thus explanatory of this distribution. Endothelium (compare the Kupffer cells in this case) is notoriously liable, together with fibrous tissue, to xanthomatous infiltrations. Only a few cases of xanthomatosis of the vascular endothelium appear to have been described in the literature. Low⁹ stated briefly that there were (clinically presumptive) xanthomatous lesions on the heart valve. Similarly, the reports of Lehzen and Knauss¹⁰ and of Pavy and Fagge,¹¹ although they described extensive yellow plaques grossly in arteries or on the mural endocardium (Balzer¹²), were not satisfying histologically, it was not clear whether the changes were xanthomatous or simply atheromatous. The situation will be illustrated at the end of the next paragraph, figure 11 illustrates clearly the difference between intimal xanthomatosis and ordinary atheroma. Although they occurred in a neoplasm, the changes which Petri¹³ described in the walls of the blood vessels of a hemangioma fully qualify as xanthomatous.

In point of extensiveness of xanthomatous changes in the internal organs, our case was excelled by that of Bross,⁵ cutaneous lesions, however, were confined to a faint, diffuse yellowing of the scrotum. As in our patient, there were yellow fleckings on the capsules of the spleen and liver and on the intima of the aorta and pulmonary arteries. The following additional lesions were described: multiple xanthomas of the kidneys, with a xanthomatous infarct of the left kidney, small xanthomatous foci in the prostate and the duodenal mucosa, lymphangiectatic

8 Pinkus F, and Pick, L. Xanthoma and Foam Cell Tumors, with Report of a Case of Generalized Xanthoma Tuberosum, *Dermat Ztschr* **15** 706, 1908

9 Low R C. Xanthoma Tuberosum Multiplex, with Lesions in Heart and Tendon Sheaths *Brit J Dermat* **22** 109 (April) 1910

10 Lehzen G, and Knauss, K. Ueber Xanthoma multiplex planum, tuberosum mollusciforme, *Virchows Arch f path Anat* **116** 85, 1889

11 Fagge, C H. General Xanthelasma or Vitiligoidea, *Tr Path Soc London* **24** 242, 1873

12 Balzer, F. Researches on the Anatomical Characters of Xanthelasma, *Arch de physiol norm et path* **4** 65, 1884

13 Petri, E. Xanthomatous Tissue Changes, Haemangioma Xanthomatousum *Zentralbl f allg Path u path Anat* **34** 1, 1923

xanthomatosis of the appendix, the mesenteric and the retroperitoneal lymph nodes and of the bone marrow of the femur. The studies were conducted under Lubarsch's direction, and the xanthomatous nature of the lesions was established histologically. Bross emphasized that the xanthomatous processes involved interstitial substance exclusively and not the parenchyma. He commented properly that there had been numerous xanthomatous fleckings described previously as occurring on the capsules of organs, but without microscopic confirmation, and that his own observations would tend to demonstrate that the previous authors were correct in regarding the fleckings as truly xanthomatous. However, the yellow lesions on blood vessels are still to be considered questionably xanthomatous, as the lesions in his patient proved, under the microscope, to be at times xanthomatous and at other times simply atheromatous.

In Christian's disease the xanthomatous infiltrations are more widespread, in general, than in any other expression of xanthoma, flat bones, lungs, liver, spleen and brain are involved. This disease affects children almost exclusively, and has such a high mortality that numerous necropsy studies have been made possible. In these cases the blood cholesterol value runs exceedingly high, as much as 397 mg per hundred cubic centimeters and more. Rowland^{13a} entertained the belief that the disease is a dyslipoidosis essential to the reticulo-endothelial system. In the case which Weidman and Freeman¹⁴ described as one of xanthoma tuberosum, and which can be admitted as one of Christian's disease, it was felt that the basic lesion was granulomatous and that xanthomatous infiltration was superadded. It is conceivable that the widespread visceral involvement in Christian's disease is explainable by the youth of the tissues concerned, i. e., the tissues of young persons being comparable to the tissues of a young scar, and the tissues of old persons to those of old scars.

Although necropsy was performed in one of Fletcher's¹⁵ cases, xanthomatous change was reported only in the bile ducts, as in our case, both the intrahepatic and the extrahepatic ducts were involved.

Between the skin and the internal tissues there appears to be no correspondence in the extent of xanthomatous involvement. For example, in Bross' case of most extensive internal xanthomatosis only a mild, diffuse yellowing externally, confined to the scrotum, was noted. In Christian's disease, with its extensive osseous involvement, the skin has

13a Rowland, R. S. Christian's Syndrome and Lipoid Cell Hyperplasia of the Reticulo-Endothelial System, *Ann Int Med* **2** 1277 (June) 1929.

14 Weidman, F. D., and Freeman, W. Xanthoma Tuberosum, *Arch Dermat & Syph* **9** 149 (Feb.) 1924.

15 Fletcher, T. Xanthlasma and Chronic Jaundice. *Am J M Sc* **130** 939, 1905.

been found involved only once (Weidman and Freeman¹⁴) On the other hand, Pinkus and Pick⁸ described extensive cutaneous xanthoma and an insignificant internal one The following table is illustrative

XANTHOMATOSIS IN MALIGNANT TUMOR CELLS

Infiltration of sarcoma cells by lipoidal substances, with the production of xanthosarcomas, is well known¹⁶ Analogous developments in carcinoma cells appear comparatively seldom, a catalog of such cases will appear elsewhere¹

*Comparison of Cutaneous and Internal Xanthomatosis**

	Skin and Mucosae	Internal Lesions
Futcher ¹⁵	Eyelids, palms, elbows, etc	None mentioned
Pavy and Tagge ¹¹	Eyelids, hands, abdomen	Larynx, arteries, splenic capsule
Moxon Tr Path Soc London 24 129, 1873	Eyelids, hands, scrotum etc	Larynx, splenic capsule
Murchison Tr Path Soc Lon don 20 187, 1869	Eyelids only	Spleen and kidney
Pye Smith Guy's Hosp Rep 22 97, 1877	Eyelids only	Cancer of duodenal papilla
Pinkus and Pick ⁸	Face, trunk	None recorded
Balzer ¹²	Trunk, neck, etc	Mural endocardium
Bross ⁵	Scrotum	Vascular intima, capsules of spleen and liver, appendix, tonsil, lymph nodes, kidneys, marrow
Various authors (cited by Soc man J A M A 98 110 [Jan 9] 1932)	None mentioned, except in tooth sockets	Bones, brain, other organs irregularly involved
Weidman and Freeman ¹⁴ (case 1)	Eyelids, elbows, buttocks, etc	None
(case 2)	Eyelids, elbows, buttocks, etc	Lungs, spleen, brain, etc
Weidman and Boston (this case)	Elbows, knees, zoster scar, etc	Intima of vessels, capsule of spleen and liver
Weidman and Schaffer ¹	Eyelids, elbows, arms, scrotum, etc	Larynx, pons

* Although Gaucher's disease may not qualify as xanthoma, it should not be forgotten, with its involvement of the spleen and bone marrow (Pick Veroffent a d Kriegs u Konst Path 4 3, 1927)

White¹⁷ has emphasized the regularity with which large quantities of cholesterol were demonstrable in carcinoma, admittedly, however, the fat, if not confined to intercellular positions (which seems inconceivable), is in a different physicochemical state within the cytoplasm of ordinary carcinoma cells than it is in xanthoma cells

Cholesterol and Cell Growth—In our patient the combination of a continued and excessively high hypocholesteremia and the development of carcinoma at a relatively late stage of the hypercholesteremia must

16 Weidman, F D Xanthosarcoma of the Cheek Succeeding Xanthosarcoma of the Forearm Multiple Tumors Versus Metastasis, Arch Surg 34 792 (May) 1937

17 White C P On the Occurrence of Crystals in Tumours, J Path & Bact 13 3, 1909

recall the continuous undercurrent of thought in many quarters as to the rôle of cholesterol in furthering the growth of cancer. In the experiments of Sweet, Corson-White and Saxon¹⁸ on rats, metastases were increased tremendously when cholesterol was sprinkled on the inoculated tumor tissue. Luden¹⁹ emphasized years ago how determinations of blood cholesterol should be of special value in the study of malignant growth because cholesterol promotes the multiplication of cells. Roffo²⁰ found three times more cholesterol in the tumor tissue than in the rest of the animal. Most recently Morelli and Focosi²¹ emphasized the rôle of lipid metabolism. "The lipids of the lymphatic apparatus and of the reticulo-histiocytic system are of greatest significance for the formation of neoplasms." In short, this opinion concerning cholesterol has been asserted by such scattered and independent investigators that we cannot escape at least consideration of the rôle that lipids played in promoting the cancer in our patient. It is unnecessary to add that cholesterol cannot be the sole factor, any more than it is the sole factor in the determination of xanthomatous lesions. Nevertheless, the occurrence of cancer in this patient and of the cancers in the stomach¹ in two successive cases of xanthoma under the observation of the same physician and studied at necropsy is difficult to dismiss as a mere coincidence. This is particularly the case since the gastric carcinoma with metastases cited¹ was such an outstanding example, and since the xanthomatosis, connoting a general lipid disturbance, had been present for more than ten years.

Xanthomatosis and Tumors in General—In our patient the tumor was not xanthomatous. It is rare under any circumstances for epithelial cells to become outstandingly xanthomatous. Even in Pick's²² extensive case of osseous Gaucher's disease, which involved a widespread hyperlipoidosis, the cancer of the bile duct was not described as xanthomatous. Tumors of the connective tissue, however, are liable to the change, particularly fibrosarcomas of the tendon sheaths. Since the tumor in our patient does not bear on this subject, reference is made

18 Sweet, J. E., Corson-White, E. P., and Saxon, G. J. Relation of Diets and of Castration to the Transmissible Tumors of Rats and Mice, *J. Biol. Chem.* **15** 181 (July) 1913.

19 Luden, G. Cancer and Chemistry, *Woman's M. J.* **30** 1 (Jan.) 1923, Blood Cholesterol. Its Importance and the Value of Its Determination in Cancer Research, *Canad. M. A. J.* **12** 147 (March) 1922.

20 Roffo, A. H. Cholesterol Ratio in Tumors, *Prensa med. argent.* **11** 1060 (April 20) 1925.

21 Morelli, E., and Focosi, M. Changes in Lipoid Metabolism Following Treatment with Cancer-Forming Substances, *Ztschr. f. Krebsforsch.* **34** 473 (Oct. 17) 1931.

22 Pick, L. The Skeletal Form of Gaucher's Disease, *Veröffentl. a. d. Kriegs- u. Konstitutionspath.* **4** 3, 1927.

here only to other conditions (xanthosarcoma¹⁶ and cancer of the stomach¹⁷) mentioned in the literature on xanthomatous tumors in general

Suppurative Features—Mention has already been made that a number of the xanthomatous lesions became suppurative, and that a small abscess developed in the lobe of the ear, apparently independent of a xanthomatous nodule. It was likewise stated that in the histologic sections of a xanthomatous nodule there was a perifollicular, polymorphonuclear infiltrate. This phenomenon, i.e., the complicating suppuration, is rare if not unique for xanthomatous nodules. Under these circumstances, the presence of a focus of extreme polymorphonuclear infiltration adjacent to the biliary neoplasm, together with the obvious stasis in the biliary tract, appears to be of importance. That is, it is surmised that the biliary lesion represented a focal infection from which a state of subinfection (in the sense of Adams) was induced, with localization thereafter in an abnormal focus such as a xanthomatous nodule.

In the last-named connection, a second interpretation must also be recorded, namely, that the cutaneous xanthomas began as microscopic abscesses—cutaneous metastases from the focal infection in the biliary tract. Under these circumstances, fibroblasts developed, which in the presence of a hypercholesterolemia took on the character of xanthoma cells. While this explains the cytologic phases in the situation, it does not explain the distribution of the lesions, i.e., the predilection for the elbows and the knees. The latter distribution, however, was still not an exclusive one, other nodules were scattered rather widely elsewhere. The success of one of us (F. D. W.²³) in one of his experiments with pneumotoxin on hypercholesteremic dogs may bespeak a toxic factor as one of several conditions which predispose cells to lipid infiltration. We lean toward this second interpretation in our case, we give emphasis to the suppurative features because it is such exceptional incidents which have value in our search for the additional *x*, *y* and *z* factors which determine the formation of xanthoma cells and which are commonly and loosely referred to collectively as predisposition.

SCAR (AND ZOSTERIFORM) XANTHOMA

Considering scars in their broadest, general pathologic, i.e., regenerative sense, there is a fairly long list of cases cited in the literature in which scars became xanthomatous. The more unequivocal examples, such as those following surgical operations and trauma, are rarer.

In Kreibich's⁷ patient a zoster developed which, from its description, almost duplicated that in our case. Thus, jaundice developed in a syphi-

23 Weidman, F. D. Studies in Hypercholesterolemia. III. Approach to the Pathogenesis of the Xanthomas, Arch. Dermat. & Syph. 15: 659 (June) 1927.

litic man who had a large, hard liver and in whom the spleen was palpable. Eventually, as in our case, the Wassermann reaction of the blood became negative. The blood cholesterol measured 750 mg per hundred cubic centimeters (normal value by his technic, 200 mg per hundred cubic centimeters). Papular xanthomas developed in groups in a zosteriform band involving dermatomes from the sixth to the ninth, the illustration depicts a lesion that is practically identical with ours. Xanthomatous lesions were also present on both olecranon and knees, and the author emphasized the follicular character of many of the nodules. (The interpretation he placed on the latter was different from ours, it will be recalled that we believed that those in our patient were referable to minute traumatism inflicted during shaving. Kreibich thought that the lesions were due to toxic nervous impulses.) Although he cited the rôle of gastric crises (ulcer, cancer, vomiting and tabes) in the development of zoster, it appears that a final opinion was not arrived at as to the exact nature of the gastric lesions in his patient.

The effect of Kreibich's experience was that we attributed the development of the zoster lesion in our patient to an analogous origin in the gastro-hepatic region, most reasonably the polyp at the ampulla of Vater. If this is admissible, it would go far toward establishing the age of the carcinoma in our patient, about which we have been so much perplexed. Since the zoster lesion occurred at the fourth month of the disease, it will be reasonable to suppose that the polyp likewise was present at least that early.

Kreibich also expressed a number of new thoughts in respect to the etiology of xanthoma. The zosteriform lesions in his patient were not inflammatory. Hence he assumed that they were referable not to inflammation but to exalted tonus of the skin cells induced by exaggerated efferent impulses which in the final analysis emanated from the stomach, that is, the xanthoma lesions had a morbid-physiologic rather than a material basis in causation. He explained the follicular distribution on the same basis—that it was due to physiologic stress put on the hairs, that is, a lesser grade of stimulus than that of inflammation sufficed to initiate the xanthomatous processes. Kreibich cited the acne zosteriformis of Blaschko as analogous to his zosteriform xanthoma, which, it appears, is also due solely to nerve stimuli.

As Kreibich did not record the history of the development of the zosteriform lesions, it is probable that they were not observed by a dermatologist at the beginning. It is thus possible that the original lesions were red papules, i.e., abortive zoster as in our case, and that by the time they came under Kreibich's observation they were papular xanthomas. Again, the acneform arrangement of Blaschko's acne zosteriformis could, similarly, be explained as the consequence of zosteriform scars the contractions of which had widened the follicular orifices.

Hardaway²⁴ also mentioned a zosteriform arrangement as part of a xanthomatosis involving the mucosae, tendons and subcutaneous tissue. Only an abstract of his paper was published, hence one cannot compare his case with ours and analyze it in the modern light. Hepatic disease was present, however, and Hardaway remarked that the zosteriform xanthomas "might have resulted from an abortive attack of herpes zoster."

To return to scars proper, the most fully studied case we found was that of Urbach²⁵. In the scar of a tuberculo-ulcerous syphilitic he observed the development of fifteen xanthomatous nodules. A most comprehensive chemical study of the blood and other fluids was made, but no abnormalities were found, the blood cholesterol was well within the normal limits on two examinations. In short, the xanthomas developed in syphilitic scars in the absence of a hypercholesteremia or other demonstrable metabolic upsets. Urbach concluded that the source of the fat was in the local inflammatory-degenerative processes existing at the site of the syphilitic process (an age-long theory), and that in the presence of a lipid surcharged serum in this situation the fibrous tissue cells absorbed the fat.

One of us (F. D. W.) presented for Gittings²⁶ at a meeting of a dermatologic society a child, aged 3 years, in whom there were highly developed xanthomatous lesions in a laparotomy scar and in the gums, in the latter site succeeding the extraction of teeth. The patient was presented both for this reason and because similar changes were absent in *old* scars, such as those at the umbilicus and at the site of an antismallpox vaccination. The blood cholesterol value for this patient was 1,067 mg per hundred cubic centimeters. The case will be reported in full by Weidman and Stokes²⁷.

Posner,²⁸ too, reported briefly and incidentally the development of a laparotomy scar richly studded with xanthomatous nodules in a woman, aged 37. The nodules were particularly conspicuous in the stitch holes.

24 Hardaway, W. A. Xanthoma Multiplex of Skin Mucosæ, *J. Cutan. & Ven. Dis.* **2** 353, 1884.

25 Urbach, E. True Xanthoma or Xanthomatosis Degeneration of the Skin, *Klin. Wchnschr.* **2** 542, 1923.

26 Gittings, J. C. Xanthoma Tuberosum with Jaundice, *Arch. Dermat. & Syph.* **17** 730 (May) 1928.

27 Weidman, F. D., and Stokes, J. Extensive Xanthoma Tuberosum in Childhood Due to Infectious Cirrhosis of the Liver, *Am. J. Dis. Child.* **53** 1230 (May) 1937.

28 Posner, O. Symptomatic Xanthoma in Chronic Icterus, *Deutsche med. Wchnschr.* **35** 96, 1909.

Although he did not see the patient, Schmidt²⁹ reported numerous xanthomas in a scar made by an excision, the case came to his notice when the blood was referred to him for examination. The blood cholesterol measured 194, 392 and 414 mg per hundred cubic centimeters at different periods.

Ochs³⁰ presented a girl, aged 7 years, at a meeting of a dermatologic society. In addition to lesions on the fingers and elbows, there were a few on the buttocks at the site of former therapeutic antisiphilic injections. The injections were made at the age of 9 months. In a personal communication, Ochs added that the Wassermann test of the blood was negative, and that the skull, elbows, wrist, feet and all bony structures were normal roentgenologically, i. e., that the condition was not Christian's disease. Blood cholesterol measured 800 mg per hundred cubic centimeters, lecithin, 367.5 mg, uric acid, 2.9 mg, urea nitrogen, 10.8 mg, sugar, 75 mg, and chlorides, 526 mg. Two of the physicians who commented on his presentation felt that the site of the nodules was not at the points of injection, nevertheless, Ochs' view was strengthened by the presence of additional xanthomatous lesions around the scar caused by vaccination, which is rather conclusive. This brought the condition unequivocally into the category of xanthoma developing from scars.

In the same category belong the xanthomas which Major³¹ recorded as developing around mosquito bites on the forehead of a diabetic boy of 16. The blood cholesterol in this case was 400 mg.

Papular xanthoma developed in and around a scar following an operation for hernia on a child, aged 11 years (Artom³²). A widespread erythrodermia developed subsequently, when it disappeared, numerous xanthomatous papules remained. Here again, youthful tissues were concerned.

From xanthoma occurring in scars, which may be regarded as such in the strictest sense, it is but a step to the development of xanthoma in reactive tissue incidental to inflammatory skin lesions.

Pinkus and Pick's⁸ patient, who was xanthomatous after recovering from an intercurrent attack of erysipelas, exhibited a residual, diffusely xanthomatous skin at the site of the erysipelatous lesion. At necropsy, Hanot's cirrhosis, pneumonia, diffuse pulmonary tuberculosis, a tuberculous pericarditis and peritonitis, tuberculosis of the spleen, internal

29 Schmidt, E. The Xanthoma Question, *Arch f Dermat u Syph* **140** 408, 1922.

30 Ochs, B. Xanthoma Tuberosum, *Arch Dermat & Syph* **22** 922 (Nov) 1930.

31 Major, R. H. Xanthoma Diabeticorum, *Bull Johns Hopkins Hosp* **35** 27, 1927.

32 Artom, M. Papular Xanthoma, *Gior ital di dermat e sif* **68** 1060, 1927.

pachymeningitis and cholelithiasis were revealed. No statement was made as to the cholesterol content of the blood.

A more tardy development of xanthomas was observed by Lehzen and Knauss¹⁰ in two sisters, aged 9 and 11. The younger child had festers all over the body at 3, the xanthomas appearing at 4. The other sister had suffered a vesicular eruption preceding the xanthomas, but a useful dermatologic history could not be obtained.

Weidman's²³ observations on an experimentally cholesterolized dog in part paralleled the foregoing experience, a diffuse xanthomatous infiltration developed in an intercurrent cellulitis of the scrotum. It is curious that in spontaneous xanthomas of man the scrotum is also commonly affected.

Likewise, but not quite so clearly, a case of xanthoma with secondary keloids may belong in this series of cases of xanthoma developing in scars. Legendre, Joltrain and Levy-Franckel³³ called attention to xanthomas of the arms, forearm and hands, however, they contended that the associated keloids were secondary. They studied their patient exhaustively, the blood cholesterol measured 300 mg per hundred cubic centimeters and the total fat from 4,121 mg to 5,545 mg. The serum was milky at all times, regardless of the diet and the time of day. These investigators injected the lipoidal extract from the serum into the skin of rabbits, following which a nodule that seemed to be sclerosed developed. A photograph of the arm showed typical linear keloids, with xanthomatous nodules in the adjacent vicinity. One would be tempted, indeed, to conclude that the sequence of events in this case had been like that in Urbach's case—that the xanthomas were secondary—were it not that the studies were evidently carefully conducted. Thus, in observing the development of a keloid, the authors found that it began as a macule and changed first to a tubercous papule, then to a xanthomatous plaque and thereafter to fibrous and keloidal plaques. They emphasized that the keloids were secondary, not primary, lesions.

Pathogenesis of Xanthomatous Scars—In an attempt to reproduce scars experimentally, one of us (F. D. W.²³) induced them in ten hypercholesteremic volunteers by surgical removal of biopsy material from the elbow. All the subjects were elderly and affected with nephritis, arteriosclerosis or diabetes—diseases liable to complications by hypercholesteremia. Although the values for blood cholesterol ranged between 264 and 448 mg per hundred cubic centimeters, xanthomatous lesions did not develop, nor were xanthoma cells found in the excised skin, even in the face of such a high concentration of blood cholesterol. It is generally agreed that hypercholesteremia alone cannot account for the development of xanthomas, the appropriate conditions in cellular metabolism

³³ Legendre, R., Joltrain, E., and Levy-Franckel, G. Xanthoma General and Disseminated with Secondary Keloids, *Bull. med., Paris* **26** 1043, 1912.

must accompany it, and it appears that these do not regularly obtain in simple uncomplicated regeneration such as occurs in clean surgical wounds. The development of xanthomatous changes resides as much in the cell as in the fluid in which the cell is reared.

Hermann and Nathan³⁴ had the same experience, in a boy with hundreds of xanthomatous nodules there was no development of xanthoma in a 2 year old scar. Likewise, in a sister of about the same age none developed in scars caused by biopsy. The brother did not exhibit hypercholesteremia, but the sister's blood yielded a cholesterol value ranging between 300 and 580 mg per hundred cubic centimeters on five different occasions.

With this information, the way to an understanding of the mechanism of the development of xanthomas in scars is clearer. To begin with, Anitschkow³⁵ showed in the beginning of the knowledge of xanthomatous changes that fat could be demonstrated within granulation tissue cells of healing wounds in *normal* rabbits. However, if hypercholesteremic rabbits were employed, the fats in these cells were found to be lipid, i. e., they contained cholesterol (presumably) rather than neutral fats. His classic experiment, employing seta (bits of cork dipped in turpentine), led to the development of xanthomatous cells, this, in principle, may be regarded as the development of xanthomatous changes in scars. One may surmise that *young* fibrous connective tissue cells are members of a group of cells which have an inherent propensity to take up fatty substances from the environment.

In the development of the xanthoma cell per se, the original source of the lipids, whether local or part of a general hyperlipidosis, is not pertinent. Stewart³⁶ compiled a long list of local lesions (local in the sense that the hypercholesterosis is not generalized as part of an associated hypercholesteremia), such as dermoid cysts and galactoceles, in which xanthoma cells will be found. That is, local conditions may account for an excess of lipids, such as obtain in connection with inflammatory and associated degenerative processes, under the influence of which the immersed, actively growing fibrous tissue cells become stored and swollen with lipids. This would explain the xanthomas in the syphilitic scars which Urbach²⁵ described, and with which there was no associated hypercholesteremia.

On the other hand, wherever there is general hyperlipidosis, local lymphatic saturation is guaranteed, and it is then necessary only to add

34 Hermann, F, and Nathan, E. Genesis of Xanthomas, Arch f Dermat u Syph **152**:575, 1926

35 Anitschkow, N. H. Experimental Investigation on the Deposition of Cholesterol in Subcutaneous Tissue, Arch f Dermat u Syph **120** 627, 1914

36 Stewart, M. J. On the Cellular Reactions Induced by Local Deposits of Cholesterol in the Tissues, J Path & Bact **19** 305, 1915

appropriate local conditions in respect to fibrous and other cells to understand the development of a local xanthomatous focus. This was the situation in Gittings' case, in Pinkus and Pick's case of erysipelas, in the experimental dog studied by one of us (F D W) and in our case of zoster. If one is to accept the opinion of Legendre, Joltrain and Levy-Franckel, namely, that the keloids succeeded xanthoma, one must conclude that the formation of a scar did not enter into the xanthomatous aspect of his case, i e., that these scars were sequelae and were residual after the xanthomatous infiltrations had become absorbed.

For the sake of convenience in clinical expression, we propose here-with the designation "scar xanthoma" in cases in which scars are in any way concerned in xanthomatous processes. As already indicated, scar xanthomas may occur entirely apart from hypercholesteremia, or, being part of a general hypercholesteremia, may be of diagnostic value and point in the direction of a grave fault of metabolism which in turn may be referred to important anatomic disease. Attention is called to the ages (3, 7 and 11 years) at which some of the scar xanthomas developed.

Operative Intervention in Xanthomas—This is generally directed at the biliary tract in view of the jaundice which usually attends, i e., quite regardless of the associated xanthomatosis. Only a few cases have been reported.

The exploratory laparotomy performed on Weidman and Stokes' ²⁷ patient was in the nature of removal of tissue for biopsy, hepatic tissue was obtained for histologic examination.

The lesion at the duodenal papilla in our patient was so indefinite that it was not identifiable as cancer at either operation or necropsy. In any event, the cardiac failure which overtook the patient prevented a just estimate of what the surgeon might achieve with a fair opportunity. Incidentally, although the patients were not operated on, one should remember that cancerous lesions at the duodenal papilla have been met in previously reported cases of xanthoma (Pye-Smith's ³⁷ case at necropsy and Moxon's ³⁸ case of a noncancerous stricture). As to the cutaneous involvement in these cases, only the eyelids were affected in the first, but the xanthomatous lesions were extensive in the second. Cancer of the bile duct was also associated in one of Pick's cases of skeletal Gaucher's disease, which is related at least to xanthoma, although there were no cutaneous lesions.

In three instances the patients survived operation. In Wijnhausen's ³⁹ patient, traumatic pancreatitis was largely corrected, interest-

37 Pye-Smith, P. Vitiligoidea or Xanthoma, *Guy's Hosp Rep* **22** 97, 1877.

38 Moxon, W. Simple Stricture of the Hepatic Duct, Causing Chronic Jaundice and Xanthelasma, *Tr Path Soc London* **24** 129, 1873.

39 Wijnhausen, O. J. Xanthomatosis in Recurrent Pancreatitis, *Berl klin Wchnschr* **58** 1268, 1921.

ingly, crops of xanthomas preceded the several abdominal crises which were incidental to the pancreatitis. One of Fitcher's¹⁵ patients, who had an extensively xanthomatous involvement dermatologically, was cured after the removal of gallstones. A second, with only xanthoma of the eyelid, was not improved. There was hypertrophic cirrhosis without gallstones. Posner's²⁸ experience was almost identical.

In the laryngeal cases of Finney⁴⁰ and of Pusey and Johnstone,⁴¹ tracheotomy became necessary. It may be added that xanthomas also occurred on the gums and in the laparotomy scars in certain of the aforementioned cases in which operation had been resorted to.

SUMMARY AND CONCLUSIONS

In connection with an extreme hypercholesteremia (1,020 mg per hundred cubic centimeters) in a patient with generalized xanthoma tuberosum, an acute xanthoma succeeded an intercurrent herpes zoster. At necropsy, severe biliary cirrhosis was found, which explained the hypercholesteremia. A polyp at the duodenal papilla was probably the primary factor in the disease complex. Since the polyp eventuated in adenocarcinoma, attention is recalled to the rôle of cholesterol in promoting cell division and possibly cancerous hyperplasia.

In addition to cutaneous xanthomatosis, the deposits also occurred internally. They appeared as plaques (in relationship with endothelium) on the splenic and hepatic capsules, in the intima of the great vessels of the neck and in the muscular tunic of the intestine. The tabulation given shows the range of cutaneous and visceral involvements in all of the reports of necropsy available.

The lipids of the xanthoma cells were preeminently neutral fats and not the cholesterol esters suggested by the hypercholesteremia and emphasized in the older literature.

Cutaneous xanthomatosis should prompt examination first, not alone of the cholesterol content of the blood but of the lipids in general. Thereafter search should be made in respect to all conceivable causes already established for hepatic disease.

Instances of scar xanthoma are collected and analyzed, actively growing fibrous tissue, whether in a local scar or in juvenile patients in general, appears to contribute factors leading to the development of

40 Finney, W. P. Xanthoma Multiplex with Involvement of the Upper Part of the Respiratory Tract, *Proc. Staff Meet., Mayo Clin.* **6**: 667 (Nov. 11) 1931.
Finney, W. P., Montgomery, H., and New, G. B. Xanthoma Multiplex, *J. A. M. A.* **99**: 1071 (Sept. 24) 1932.

41 Pusey, W. A., and Johnstone, O. P. A Case of Xanthoma Diabeticorum and Lipoma Multiplex and a Case of Xanthoma Approaching the Diabetic Type with Diabetes Insipidus, *J. Cutan. Dis.* **26**: 552, 1908.

xanthoma cells The cells in old scars and in simple regeneration do not tend to become xanthomatous The application of this observation to spontaneous xanthomas is pointed out, i e, that a preceding dermatosis may in some cases be the incitant to the formation of xanthoma To what extent this operates remains to be determined Local cutaneous suppuration, present in our patient, may have been the incitant to xanthomatous formation by provoking the formation of young fibrous tissue

Instances of surgical intervention in connection with xanthoma are collected and abstracted Marked improvement succeeded in only one case

NITROGEN AND SULFUR METABOLISM IN BRIGHT'S DISEASE

VIII EFFECT OF INGESTION OF UREA ON NITROGEN EXCRETION AND SULFUR PARTITION IN NEPHROSIS, GLOMERULO- NEPHRITIS AND CIRRHOSIS OF LIVER

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Previous studies have called attention to the strongly positive nitrogen and sulfur balances in patients with the nephrosis syndrome¹ and to the tendency to negative balances in patients with chronic glomerulonephritis². More recently retention of urea was noted in a patient with nephrosis,³ confirming the earlier observations of Peters⁴. Later observations by Peters⁵ were interpreted by him as indicating a similar retention of urea fed to normal subjects, though of lesser degree than was the case in patients with nephrosis. These conclusions were contested by Kocher and Torbert,⁶ who, however, failed to repeat Peters' experimental conditions, as they studied subjects on protein-free diets whereas all the other experiments were done by feeding urea to subjects on an adequate mixed diet. It seemed desirable to see if further experiments could be devised to reconcile the contradictory findings, which may be summarized as follows. Peters reported the retention of huge amounts of crystalline urea fed by mouth to patients with so-called chronic nephrosis. In a recently published case we have confirmed these findings. On the other hand, Peters reported the retention of small amounts of urea fed to the normal human subject. His findings in the normal subject were explained by Kocher and Torbert by calling attention to the delayed excretion of the extra urea in Peters' experi-

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1 Grabfield, G P J Clin Investigation **9** 311, 1930

2 Grabfield, G P J Clin Investigation **10** 309, 1931

3 Grabfield, G P Nitrogen and Sulphur Metabolism in Bright's Disease IV Retention of Urea in the Nephrosis Syndrome, Arch Int Med **52** 632 (Oct) 1933

4 Peters, J P, and Moore, D D J Clin Investigation **6** 5, 1928

5 Moore, D D, Laviates, P H, Wakeman, A M, and Peters, J P J Biol Chem **91** 373, 1931

6 Kocher, R A, and Torbert, H C J Biol Chem **95** 427, 1932

ments, though their own experiments were done on fasting subjects. All the studies so far lack various elements of certainty, such as analyses of the food and of the stool in some, and the experimental conditions have varied. None has included an investigation of the excretion of sulfur, and none has taken account of the proteimuria. It seemed worth while, therefore, to repeat the experiments, supplying all the missing conditions so far as possible.

In order to make this comparison, we deviated from Peters' regimen, in that our doses of urea were less, but it was not deemed advisable to give as large doses to a patient with glomerulonephritis as can be easily taken by patients with nephrosis, for example. It therefore seemed desirable to give the same dose of urea (20 Gm a day) throughout all the experiments. We carefully selected two patients whose conditions represented as nearly pure examples of the nephrosis syndrome and glomerulonephritis as was possible. As we have previously presented evidence suggesting that an extrarenal mechanism might explain the metabolic findings, it seemed desirable also to include a patient presenting a classic picture of alcoholic hepatic cirrhosis. As a further control, one of us was studied on the regimen to be outlined presently. The important differentiating laboratory findings in these cases are presented in table 1. Case histories and detailed results of the experiments are also included. The purpose of this regimen was to provide an adequately balanced diet which would have the minimum of chemical variation from day to day. It was evident that such a condition could be best obtained by feeding exactly the same foods in constant amounts every day of the experiment. Such a diet is monotonous, and only the perfect cooperation that we obtained from the patients and the dietitians enabled us to use these ideal experimental conditions. Careful investigation by the dietitians of the patients' likes and dislikes enabled them to provide a diet that the patients were able to eat for four weeks. Care was taken to provide the same cut of meat and similar portions of vegetables. The diet was calculated from standard diet tables. Duplicate diets were then prepared every day (in some experiments, twice a week) and were analyzed by periods (table 2). Care was taken to reduce loss of water in cooking to a minimum, and the duplicate diets were cooked simultaneously and in similar containers. The food was weighed before and after cooking to check the loss of water. Fluids were measured, and sufficient was given to make the daily total constant, including the amount of water in the food. No salt was used in cooking, and a weighed amount of sodium chloride was given each day. Collections of stool were made daily, the various periods being marked by carmine or charcoal. The total nitrogen and sulfur of the stool was determined from a sample of the mixed stool for the entire period. Collections of urine were made daily under toluene or preserved with thymol dissolved in chloroform. The bottle for urine was kept in an icebox by the bedside, and the patient voided directly into the bottle. Urinary analyses for creatinine, total nitrogen, urea nitrogen, amino-acid nitrogen and the complete sulfur partition were made daily, both for the urine as voided and for the filtrate after the protein had been precipitated by heat and 0.5 per cent acetic acid. The solution of urea was analyzed both for total nitrogen and for urea, and it contained by analysis 497 mg against a theoretical 500 mg in the samples analyzed. In the calculations we have used the theoretical nitrogen content.

Standard methods of analysis were used the Folin⁷ methods for creatinine, total nitrogen, urea and amino-acid nitrogen and the Fiske⁸ methods for the sulfur partition. Feces and food were dried after acidifying with hydrochloric acid and then analyzed for nitrogen by the Kjeldahl method and for sulfur gravimetrically by oxidation with sodium peroxide and precipitation as barium sulfate. The results in the individual cases are given in detail in the accompanying

TABLE 1—Data for Three Patients

	Nephrosis	Nephritis	Cirrhosis
Blood urea nitrogen, mg per 100 cc	14	11.21	11
nonprotein nitrogen, mg per 100 cc	38	35	23
total protein, Gm per 100 cc	4	6.6	7
albumin, Gm per 100 cc	1.7	3.9	4.1
globulin, Gm per 100 cc	2.3	2.7	2.9
cholesterol, mg per 100 cc	615	275	
calcium, mg per 100 cc		10.3	
phosphate, mg per 100 cc		4	
creatinine, mg per 100 cc		1.2	
Phenolsulfonphthalein excretion, percentage	45	65	
Urea clearance, percentage	88.82	80.87	
Galactose, Gm excreted in five hours			12
Bromsulphalein			Normal
Urinary albumin	Large trace	Very slight trace, slight trace	0
Urinary sediment	Double refractile lipoids	Casts, ++	0
Hemoglobin, percentage	80.100	100	55.90
Erythrocytes, million	4,155	5.4	2,745
Leukocytes, thousands	10.15	8.10	5,481

TABLE 2—Detailed Data on the Diet of Three Patients and One Normal Subject

Daily Intake	Nephrosis		Nephritis		Cirrhosis		Normal	
	From Tables	By Analysis	From Tables	By Analysis	From Tables	By Analysis	From Tables	By Analysis
Calories	2,569		2,472		2,446		2,614	
Carbohydrate, Gm	314		201		209		249	
Fat, Gm	100		148		146		147	
Protein, Gm	104	100.2	85	83.7	75	79.8	81	80.6
Sulfur, Gm	1.20	1.22	1.07	1.02	1.13	1.12	1.21	1.19
Sodium, Gm	1.25		1.16		1.25		1.50	
Chlorine, Gm	1.90		1.73		1.85		2.24	
Sodium chloride as such, Gm	2.00		1.00		4.00		4.00	
Water of food, Gm	1,665	1,653	1,541	1,643	1,551	1,646	1,697	1,674
Water as such, cc	736		1,000		1,080		1,200	
Total water intake, cc	2,401		2,541		2,631		2,897	

protocols, and summarizing tables from these results are included to facilitate discussion. In these tables the results are presented as of three periods in each case, the first being the control period, the second the period of administration of urea and the third the post-urea period. The post-urea period is divided into two

7 Folin, O. Laboratory Manual of Biological Chemistry, ed. 5, New York, D. Appleton-Century Company, Inc., 1934.

8 Fiske, C. H. J. Biol. Chem. 47: 59, 1921.

sections, the latter of which represents the return to normal and the first an intermediate period between the administration of urea and such a return. The numbers in these tables represent the average daily figure for the period.

CASE 20—A white man aged 22 first entered the hospital on Sept 21, 1933, complaining of swelling of the legs and pain in the back. He had been well until ten weeks before entry, when without previous illness or a history of medication or exposure to renal irritants, he first noticed swelling of the ankles and legs. At that time he stayed in bed under medical care, with relief of symptoms. On getting up he had an ache in the right iliac region, and the swelling reappeared. The cycle of edema when he arose and disappearance of the edema when he was in bed continued for ten weeks. He had felt listless and had had some mild headaches. Physical examination revealed tenderness on pressure in the right iliac region and edema of the ankles and apparently of the uvula. The urine showed a specific gravity of 1.025 and contained a large amount of albumin and many red blood cells and casts. The blood pressure was 134 systolic and 82 diastolic. The urea nitrogen content of the blood was 7 mg, and the nonprotein nitrogen content was 22 mg, per hundred cubic centimeters. Chemical analysis of the blood showed total protein, 4.5 Gm, albumin, 2.1 Gm, globulin, 2.4 Gm. Excretion of phenol-sulfonphthalein was 65 per cent. On August 24 the average urea clearance was 85 per cent. In September a chemical analysis of the blood showed total protein, 4 Gm, albumin, 1.7 Gm, globulin, 2.3 Gm, cholesterol, 615 mg, and nonprotein nitrogen, 38 mg, per hundred cubic centimeters. Throughout the patient's stay in the hospital there was mild leukocytosis but no anemia. The urine constantly showed a large amount of protein and a moderate number of casts. The patient was readmitted to the hospital for these experiments and showed findings that were essentially unchanged, except for a diminution in the excretion of phenosulfonphthalein to 45 per cent, which ultimately decreased to 20 per cent. He was discharged after the completion of these experiments, apparently in the same condition as on entry. He was readmitted a number of times and showed a steadily decreasing renal function. He died on Nov 11, 1935. Autopsy showed contracted kidneys typical of chronic parenchymatous nephritis.

CASE 21—A white man aged 23 was admitted to the hospital on Sept 7, 1934, for the present study. His family history was of no importance. Five years before he had bilateral otitis media and two years before scarlet fever. He had nonspecific prostatitis six months before. In August 1933 he was admitted to the surgical service of the hospital for removal of a pilonidal cyst. At that time albuminuria was noted. From that time on he was followed in the medical outpatient department. On Jan 9, 1934, examination of the blood showed total protein, 7.2 Gm, albumin, 4.1 Gm, globulin, 3.1 Gm, and nonprotein nitrogen, 20 mg, per hundred cubic centimeters. The albuminuria had persisted. Shortly before he entered the hospital for the present study he was infected over the face and right hand with poison ivy, but the inflammation had almost disappeared. Physical examination revealed dilatation of the right pupil due to medication for iritis, for which he had been treated at the Massachusetts Eye and Ear Infirmary during the ten days before his admission for the present study, otherwise there was no remarkable finding. The blood pressure was 130 systolic and 80 diastolic. The other laboratory findings are given in table 1. He remained free from symptoms during his stay in the hospital.

CASE 22—A white man aged 38 first entered the hospital on June 26, 1934, because of hematemesis three hours before. He had a syphilitic lesion in 1920, which had been treated with mercury and arsenic for two years. In 1919 and

TABLE 3—Data for Patient (Case 20) with Nephrosis

Date, 1933	Body Weight, Kg	Urine as Voided										Protein Free Urine										Pe- riod
		Creati- nine, Mg	Total Nitro- gen, Gm	Urea and Am- monia Nitro- gen, Gm	Amino Acid Nitro- gen, Mg	Total Sulfur, Mg	Total Sulfate, Mg	Inor- ganic Sulfate, Mg	Ethe- real Sul- fate, Mg	Neu- tral Sul- fur, Mg	Urine, Cc	Total Nitro- gen, Gm	Urea Nitro- gen, Gm	Amino- Acid Nitro- gen, Mg	Total Sul- fur, Mg	Total Sul- fate, Mg	Inor- ganic Sul- fate, Mg	Ethe- real Sul- fate, Mg	Neu- tral Sul- fur, Mg			
10/28-29	55.8	1,234	11.6	7.2	167	588	405	383	22	183	1,333	9.9	7.2	161	552	388	373	13	164	1		
10/29-30	56.0	1,504	11.8	7.4	201	592	467	373	94	125	1,475	8.5	7.4	197	543	425	354	71	118			
10/30-31	55.9	1,302	11.6	8.1	232	661	471	375	99	190	1,276	9.0	7.5	231	584	478	372	106	106			
10/31-11/1	56.2	1,637	11.5	7.9	293	761	578	496	82	183	1,723	9.2	8.2	287	689	557	441	116	132			
11/1-2	56.2	1,189	12.3	7.4		763	512	466	46	256	1,600	8.9	7.4		717	502	455	47	215			
11/2-3	56.2	1,224	16.1	11.8	175	381	364	331	33	17	1,506	14.2	11.3		390	360	329	31	30	2		
11/3-4	56.4	1,250	16.4	13.1	199	361	329	280	19	35	1,563	14.1	13.4		343	320	295	25	23			
11/4-5	56.2	1,279	18.2	12.9		750	541	465	79	206	1,752	14.3	12.9		751	533	470	63	218			
11/5-6	56.2	1,248	25.1	14.7		731	520	501	16	231	1,804	15.0	14.0	215	740	520	505	15	220			
11/6-7	56.2	1,182	24.0	15.1		761	542	530	22	222	1,566	15.8	14.9		702	526	506	20	176			
11/7-8	56.0	1,266	24.5	16.7		737	560	510	50	177	1,594	17.9	16.5	211	690	530	490	40	160	3		
11/8-9	55.8	1,154	22.8	14.7		759	550	467	83	209	1,482	17.2	15.0		750	560	466	94	190			
11/9-10	55.6	1,345	15.5	11.0		475	428	337	91	47	1,485	12.0	11.0		452	427	356	71	25			
11/10-11	55.6	1,262	14.6	8.6		491	388	308	80	103	1,395	9.3	8.9	271	458	379	290	89	79			
11/11-12	55.8	1,256	12.7	8.1	162	565	442	359	83	123	1,430	11.4	8.2	136	499	394	343	51	103			
11/12-13	56.2	1,252	12.7	8.3		630	451	410	41	199	1,270	9.5	7.8	208	570	447	390	57	123	3		
11/13-14	56.4	1,740	11.3	8.3	228	676	456	422	34	220	1,500	9.8	8.5	230	676	451	427	24	219			
11/14-15	56.4	1,288	11.8	8.2	183	554	462	415	47	92	1,442	9.0	8.1	163	526	433	401	32	93			
11/15-16	56.4	1,265	11.9	8.0	202	525	430	390	40	95	1,486	9.1	8.3	207	504	428	380	18	76			

TABLE 4—Data for Patient (Case 21) with Glomerulonephritis

Date, 1931	Body Weight, Kg	Urine as Voided										Protein Free Urine										1
		Creatl nine, Mg	Total Nitro- gen, Gm	Urea and Amo- nia		Total Sulfur, Mg	Total Sulfate, Mg	Inor- ganic Sulfate, Mg	Ethhe- real Sul- fate, Mg	Neu- tral Sul- fur, Mg	Urine, Cc	Total Nitro- gen, Gm	Urea Nitro- gen, Gm	Amino Acid Nitro- gen, Mg	Total Sul- fur, Mg	Total Sul- fate, Mg	Inor- ganic Sul- fate, Mg	Ethhe- real Sul- fate, Mg	Neu- tral Sul- fur, Mg			
				Nitro- gen, Gm	Nitro- gen, Mg																	
9/11 12	51.8	987	13.1	10.4	125	1,292	1,192	1,093	94	100	1,880	12.2	10.5	125	1,245	1,180	1,083	97	65			
9/12 13	51.8	935	13.2	10.5	130	1,299	1,187	1,089	98	112	1,950	12.3	10.4	130	1,241	1,157	1,079	78	84			
9/13 14	51.2	1,086	13.4	10.8	131	1,307	1,201	1,110	91	106	2,150	12.6	10.8	131	1,262	1,150	1,072	78	112			
9/14 15	51.6	903	13.4	10.8	136	1,315	1,210	1,104	106	105	2,090	12.4	10.8	136	1,254	1,102	1,064	98	92			
9/15-16	51.6	1,009	12.9	10.4	128	1,215	1,113	1,023	90	102	1,740	12.2	10.2	128	1,195	1,100	1,002	98	95			
9/16 17	51.6	1,010	12.9	10.3	127	1,231	1,119	1,037	82	112	2,050	12.1	10.3	127	1,165	1,085	1,000	85	80			
9/17 18	52.0	1,034	21.6	18.3	130	1,285	1,195	1,115	80	90	2,080	19.5	18.3	130	1,175	1,095	1,002	93	80			
9/18 19	52.1	1,107	22.0	18.0	132	1,305	1,213	1,123	90	92	2,550	20.9	18.0	132	1,249	1,190	1,105	85	59			
9/19 20	51.4	1,074	24.2	20.3	132	1,322	1,221	1,130	91	101	2,760	21.5	20.3	132	1,180	1,084	1,004	80	96			
9/20 21	51.4	1,085	19.7	16.8	139	1,301	1,206	1,122	84	95	2,010	18.1	16.8	137	1,220	1,125	1,040	85	95			
9/21 22	51.4	1,160	23.7	19.9	134	1,312	1,227	1,135	92	85	2,500	21.0	19.9	134	1,183	1,093	1,009	89	85			
9/22 23	52.0	1,100	22.9	19.0	133	1,298	1,206	1,116	90	92	2,440	20.3	19.0	133	1,170	1,080	1,002	78	90			
9/23 24	52.0	1,097	22.5	18.5	131	1,284	1,200	1,120	80	84	2,345	20.4	18.5	131	1,181	1,101	1,019	82	80			
9/24 25	51.8	1,114	15.6	12.5	131	1,313	1,222	1,132	90	90	2,350	14.9	12.5	131	1,280	1,190	1,102	83	90			
9/25 26	51.8	1,033	12.1	10.0	134	1,264	1,176	1,091	85	88	2,050	10.9	10.0	134	1,203	1,114	1,029	85	89			
9/26 27	51.6	1,041	12.9	10.2	131	1,252	1,160	1,076	84	92	2,150	12.0	10.2	131	1,205	1,125	1,040	85	80			
9/27 28	51.4	1,044	13.0	10.4	130	1,283	1,198	1,116	82	85	1,725	11.9	10.4	130	1,238	1,149	1,061	88	89			
9/28 29	51.8	1,068	13.1	10.0	130	1,293	1,206	1,121	85	87	1,940	10.6	10.0	130	1,182	1,087	1,012	75	75			
9/29 30	51.8	1,059	13.1	10.3	135	1,308	1,223	1,143	80	85	2,300	12.0	10.3	136	1,231	1,190	1,105	85	61			
9/30 10/1	52.0	1,064	13.0	10.1	136	1,327	1,242	1,161	81	85	2,000	12.1	10.1	136	1,277	1,197	1,101	96	80			

again in 1932 he had also had gonorrhea. He had always been a heavy drinker, particularly in the last two years. During the last two or three months he had consumed from a pint (473 cc) to a quart (946 cc) of whisky a day. He dated his present illness from February 1934, when he noticed the onset of weakness and loss of ambition. During the last two months he vomited every morning. Three hours before he entered the hospital he drank a pint of whisky and one hour later vomited what he estimated to be a quart of blood.

Physical examination showed that he was pale and had a clammy skin. The blood pressure was 106 systolic and 86 diastolic. The spleen was enlarged to percussion. The edge of the liver was felt 9 cm below the costal margin. The patient had some delusions at night, which a psychiatrist believed were due to alcohol. A blood count showed 2,600,000 erythrocytes. Esophageal varices could not be demonstrated roentgenographically. No lesions were observed in the gastro-

TABLE 5—Data for Patient (Case 22) with Cirrhosis of Liver

Date, 1934	Weight, Kg	Urine, Cc	Creati- nine, Mg	Total Nitro- gen, Gm	Urea Nitro- gen, Gm	Amino Acid Nitro- gen, Mg	Total Sul- fate, Mg	Inor- ganic Sul- fate, Mg	Ethe- real Sul- fate, Mg	Neu- tral Sul- fur, Mg	Total Sul- fur, Mg	Pe- riod
7/31 8/1	67 0	900	1,296	8 3	6 1	165	616	561	55	70	686	1
8/ 1 2	67 2	795	1,324	8 7	6 8	159	618	570	48	75	693	
8/ 2 3	67 4	690	1,354	8 7	5 5	149	615	564	51	61	676	
8/ 3 4	67 6	1,090	1,134	8 3	6 4	149	619	577	42	43	662	
8/ 4- 5	67 8	1,200	1,212	8 3	6 3	149	618	581	32	50	663	
8/ 5 6	67 4	1,900	1,164	9 5	8 7	155	861	790	71	40	901	
8/ 6 7		1,175	960	12 8	9 9	150	682	614	68	79	761	2
8/ 7 8	67 6	900	1,062	14 8	12 4	150	679	610	69	75	754	
8/ 8 9	67 8	1,200	1,061	24 2	15 9	151	676	607	69	81	757	
8/ 9 10	68 2	1,118	1,075	18 2	14 7	155	680	612	68	85	765	
8/10 11	68 2	805	1,055	13 0	10 2	152	661	600	61	80	741	
8/11 12	68 2	1,425	1,060	15 8	13 2	150	685	615	70	71	756	
8/12 13	68 4	1,860	1,147	12 8	10 7	160	782	701	81	70	852	3
8/13 14	68 4	1,550	1,149	8 4	7 2	151	655	595	60	50	705	
8/14 15	68 8	1,080	1,065	8 5	6 2	149	627	582	45	46	673	
8/15 16	68 0	1,600	1,064	7 3	5 8	159	769	700	69	91	860	
8/16-17	68 4	1,675	1,080	11 8	8 7	153	748	688	60	80	828	
8/17-18	68 5	965	1,062	8 8	6 2	151	651	602	49	48	699	
8/18-19	68 2	600	1,062	8 8	6 3	151	644	599	45	48	692	

intestinal tract. Lumbar puncture showed that the fluid was normal. The urine showed no abnormality, and the blood count rapidly returned to normal. The course during the patient's stay in the hospital was uneventful. At the time of his discharge, on August 21, the only abnormal physical sign was the enlargement of the liver, the edge of which could be felt 4 cm below the costal margin.

OBSERVATIONS AND COMMENT

As can be seen from table 7, our results confirm previous observations as to the retention of nitrogen and urea in nephrosis. Since we were able to confirm these results under the present experimental conditions, in which every possible factor was rigidly controlled, doubt as to technical errors must be excluded from consideration. It is evident also that the earlier observations on the excretion of ingested crystalline urea by a normal subject can be substantiated. In the urine and feces of our normal control we were able to account for all the urea fed

save 0.4 Gm per day, which is the amount usually stated to be excreted in the sweat. This experiment was carried out in July, and the subject was not in bed, so that this loss in the sweat is entirely reasonable.

TABLE 6—Data for Normal Subject

Date, 1934	Body Weight, Lb	Urine, Cc	Creatinine, Mg	Total Nitrogen, Gm	Urea Nitrogen, Gm	Amino Acid Nitrogen, Mg	Total Sulfate, Mg	Inorganic Sulfate, Mg	Ethereal Sulfate, Mg	Neuronal Sulfate, Mg	Total Sulfate, Mg	Period
8/8-9	160	980	1,205	11.6	9.8	163	1,141	1,080	61	65	1,206	1
8/9-10	160½	1,205	1,199	11.8	10.0	164	1,147	1,085	62	65	1,212	
8/10-11	160	1,276	1,193	11.7	10.0	158	1,149	1,075	74	52	1,201	
8/11-12	160	1,435	1,191	11.8	10.0	158	1,156	1,091	65	65	1,221	
8/12-13	161	1,210	1,204	12.0	10.2	162	1,140	1,069	71	73	1,213	2
8/13-14	160	1,550	1,291	17.7	14.6	155	1,160	1,079	81	72	1,232	
8/14-15	160	1,595	1,222	21.9	18.6	159	1,163	1,095	68	65	1,228	
8/15-16	161½	1,110	1,211	20.4	18.4	159	1,143	1,065	78	63	1,210	
8/16-17	160	1,392	1,205	19.8	18.8	160	1,149	1,089	60	70	1,219	3
8/17-18	160½	1,460	1,206	19.6	18.0	164	1,116	1,051	65	72	1,188	
8/18-19	161	1,510	1,203	19.0	17.9	163	1,145	1,081	54	60	1,205	
8/19-20	162	1,235	1,212	17.9	16.1	162	1,151	1,085	66	69	1,220	
8/20-21	161	1,650	1,226	14.6	12.6	161	1,134	1,067	77	69	1,203	3
8/21-22	160	1,190	1,214	13.9	12.0	159	1,148	1,074	74	65	1,213	
8/22-23	159	1,200	1,224	12.5	10.5	160	1,140	1,070	70	71	1,211	
8/23-24	159	1,540	1,200	12.5	10.6	160	1,147	1,088	59	76	1,223	
8/24-25	160	1,125	1,226	12.7	10.7	162	1,121	1,050	71	78	1,199	
8/25-26	159½	1,481	1,220	11.4	9.4	160	1,123	1,063	60	75	1,193	
8/26-27	159½	1,189	1,201	11.3	9.4	158	1,155	1,075	80	71	1,226	

TABLE 7—Details of the Average Daily Nitrogen Balance

Subject	Period	Days	Nitrogen Intake, Gm	Nitrogen Output in Urine and Feces, Gm	Urea Output, Gm	Nitrogen Balance, Gm	Urea Balance, Gm *	Output of Protein Nitrogen, Gm	Net Nitrogen Balance, Gm
Nephrosis	1	5	15.6	12.4	7.6	+3.2	±0.0	2.7	+5.9
	2	7	24.8	21.9	14.1	+2.9	+6.5	5.5	+8.4
	3	{4	15.6	14.3	9.0	+1.3	+1.4	3.2	+4.5
		{3	15.6	12.3	8.2	+3.3	+0.6	3.3	+6.6
Glomerulonephritis	1	6	13.4	14.4	10.5	-1.0	±0.0	0.8	-0.2
	2	7	22.7	23.4	18.7	-0.7	+8.2	2.1	+1.4
	3	{1	13.4	16.5	12.5	-3.1	+2.0	0.7	-2.4
		{6	13.4	13.8	10.2	-0.4	-0.3	1.1	+0.7
Cirrhosis of liver	1	6	12.9	9.7	6.6	+3.2	±0.0		
	2	6	21.3	17.6	12.7	+3.7	+6.1		
	3	{1	12.0	13.9	10.7	-1.9	+4.1		
		{6	12.0	10.0	7.0	+2.0	+0.4		
Normal	1	5	13.0	12.9	10.0	+0.1	±0.0		
	2	7	22.3	20.6	17.5	+1.7	+7.5		
	3	{5	12.8	14.4	11.3	-1.6	+1.3		
		{2	12.8	12.5	9.4	+0.3	-0.6		

* The column headed Urea Balance shows the amount of urea nitrogen accounted for, using the excretion of urea in the first period as a base line. The second period is the one during which urea was administered.

Similarly, we were able to recover all the urea fed to the patient with glomerulonephritis. On the other hand, in the patient with nephrosis and in the one with hepatic cirrhosis it was not possible to account for the urea ingested. This leads inescapably to one of two conclusions:

Either the urea ingested is utilized in the economy or the substance is stored in the body as such. The latter denies fundamental physico-chemical considerations, in that urea is not demonstrable in the blood. In other words, if urea is retained in the body as such, it should appear in the blood, as it is so readily diffused through cellular membranes. On the other hand, it must be remembered also that urea is an obligatory end-product. If, therefore, it is not stored, it must be excreted in some combined form. This hypothesis gains support from the evident fact that the nitrogen balance is closer than the urea balance. It is also true that this is at the expense of the increased excretion of protein. It has heretofore been assumed, not unnaturally, that the positive nitrogen balance so invariably seen during the nephrosis syndrome is concerned with the replacement of the depleted serum proteins, but this explanation cannot be applied to the patient with cirrhosis, though the relation of the serum proteins is reversed in this condition.⁹ The simple replacement of serum proteins by ingested protein seems inadequate to explain the metabolic phenomena in these cases and fails to explain the utilization of urea which seems to occur. That this utilization occurs is suggested by the observation that the total nitrogen balance in the patient with nephrosis seemed closer than the urea balance during the period when urea was ingested, this approach to balance was attained at the expense of an increased excretion of protein. We believe this point to be significant, in that it suggests that the protein excreted may be an end-product of protein metabolism—a faulty one to be sure. This idea receives further support from the fact that this excreted protein is very low in sulfur, unlike the protein in other cases of albuminuria that we have studied and which have been reported elsewhere.¹⁰

When we consider the sulfur metabolism in these subjects we find that a perfect balance was attained in the normal subject (table 8). Both the patient with nephrosis and the one with cirrhosis showed a strikingly positive balance, while the patient with glomerulonephritis showed an equally important negative balance. The laws governing sulfur balance are probably similar to those regulating nitrogen balance. However, it must be remembered that there is evidence that the sulfur-rich moiety of the protein molecule has a separate metabolism from the sulfur-poor portion.¹¹ It is evident from these experiments that under pathologic conditions the two may be distinct. The patients with glomerulonephritis showed a negative sulfur balance apart from the protein

9 O'Hare, J. P., and Driscoll, Margaret, in *Medical Papers Dedicated to Henry Asbury Christian*, Baltimore, Waverly Press, Inc., 1936, p. 639.

10 Grabfield, G. P., and Prescott, B. *Studies on Nitrogen and Sulfur Metabolism in Bright's Disease. VII. Sulfur Content of Urinary Protein*, *Arch Int Med* **57** 1081 (June) 1936.

11 Lewis, H. B. *Physiol Rev* **4** 394, 1924.

excreted, and this must have come from the sulfur-rich moiety of the protein molecule or from some completely abnormal sulfur product. The latter theory is unlikely, in that the sulfur partition was unchanged from the normal. No effect on the sulfur partition was discernible as a result of the administration of urea (table 9). In all the patients except the one with nephrosis the change in balance was slight, but what change occurred was in a negative direction, which is what would be expected when the diuresis is considered.¹² The changes in the patient with nephrosis were of a much higher order and in the opposite direction, not only the period during which urea was administered but the posturea period as well showed a significant increase of an already

TABLE 8—*Data for Sulfur Metabolism* *

Subject	Period	Days	Sulfur Intake, Gm	Sulfur Output in Urine and Feces, Gm	Sulfur Balance, Gm	Protein Sulfur, Output, Gm	Net Sulfur Balance, Gm
Nephrosis	1	5	1.21	0.70	+0.51	0.06	+0.57
	2	7	1.22	0.67	+0.55	0.02	+0.57
	3	4	1.24	0.60	+0.64	0.05	+0.69
		3	1.24	0.61	+0.63	0.02	+0.65
Glomerulonephritis	1	6	1.02	1.36	-0.34	0.05	-0.29
	2	7	1.02	1.34	-0.32	0.12	-0.20
	3	1	1.02	1.39	-0.37	0.18	-0.19
		6	1.02	1.35	-0.33	0.08	-0.25
Cirrhosis of liver	1	6	1.11	0.77	+0.34		
	2	6	1.12	0.82	+0.30		
	3	1	1.12	0.91	+0.21		
		6	1.12	0.80	+0.32		
Normal	1	5	1.19	1.25	-0.06		
	2	7	1.19	1.24	-0.05		
	3	5	1.20	1.25	-0.05		
		2	1.20	1.23	-0.03		

* These data correspond to the figures shown for the nitrogen metabolism given in table 7.

important retention of sulfur. This may indicate a use of the retained urea in combination with the "extra sulfur" retained during the feeding of urea.

If the sulfur metabolism is intimately bound up with the protein metabolism (and there is no doubt that much if not all of it is), some light may be shed on these findings by a comparison of the excretion of sulfur with that of nitrogen. Indeed it may be possible by this comparison to determine whether these variations are due primarily to a pathologic protein metabolism, since in subjects under normal metabolic conditions and in a good nutritional state the nitrogen-sulfur ratio of the urine approximates that of the food or is even somewhat lower. Con-

sequently, variations in this ratio in the urine and feces suggest which part of the protein molecule is being metabolized and which is being utilized. From table 10 it will be observed that the patient with nephrosis

TABLE 9—*The Sulfur Partition Expressed as a Percentage of the Total Urinary Sulfur*

Subject	Period	Days	Total Sulfate	Inorganic Sulfate	Ethereal Sulfate	Neutral Sulfur
Nephrosis	1	5	76	65	11	24
	2	7	79	72	7	21
	3	4	84	70	14	16
		3	78	72	6	22
Glomerulonephritis	1	6	92	86	6	8
	2	7	93	85	8	7
	3	1	93	86	7	7
		6	93	86	7	7
Cirrhosis of liver	1	6	92	85	7	8
	2	6	90	81	9	10
	3	1	92	82	10	8
		6	92	84	8	8
Normal	1	5	95	89	6	5
	2	7	94	89	5	6
	3	5	94	89	5	6
		2	94	89	6	6

TABLE 10—*The Nitrogen-Sulfur Ratio*

Subject	Period	Days	Nitrogen Sulfur Ratio				
			Intake	Urine	Protein Free Urine	Feces	Total Output
Nephrosis	1	5	12.9	17.4	14.8	61.0	17.7
	2	7	20.3	32.2	24.9	26.6	32.7
	3	4	12.6	25.2	21.3		23.9
		3	12.6	20.3	16.4	19.5	20.2
Glomerulonephritis	1	6	13.1	10.4	10.0	15.0	10.6
	2	7	22.2	16.8	18.3	11.8	17.5
	3	1	13.1	11.9	11.6		11.8
		6	13.1	10.0	8.0	11.2	10.2
Cirrhosis of liver	1	6	11.6	12.0		19.7	12.6
	2	6	19.0	21.8		18.2	21.5
	3	1	10.7	16.9			15.3
		6	10.7	11.8		18.2	12.5
Normal	1	5	10.9	9.6		50.8	10.3
	2	7	18.7	16.0		50.1	16.6
	3	5	10.7	11.0			11.5
		2	10.7	9.4		50.6	10.2

Note the high ratio of the output of the patient with nephrosis

showed the highest figures in every period and that this is equally true when only the nonprotein portions of the urine are considered. Even higher figures for this value have been previously reported.¹ It should be noted also that the exhibition of urea caused a greater rise in this

ratio in the three patients than in the normal subject. Ordinarily the diuresis produced by urea would make one expect a slight increase in the excretion of sulfur, instead of which one sees by the rise in the ratio with what tenacity these patients held on to sulfur. As a further investigation, it seemed worth while to compare the excretion of inorganic sulfate with the excretion of urea. These two fractions of the sulfur and nitrogen excretion are supposed to represent the end-products of protein metabolism, and such a comparison of the ratios indicates whether the nitrogen-sulfur ratio was an adequate representation of the course of the protein metabolism in these patients and also whether the administration of crystalline urea had any effect on this metabolism. When the nitrogen-sulfur ratio of the food ingested is compared with either the nitrogen-sulfur ratio of the urine or the urea nitrogen-inorganic sulfate ratio, it is evident that only the patient with nephrosis selectively retained sulfur, and it is further evident that the administration of urea called forth a greater relative diminution in the excretion of sulfur in this patient. The relationship of urea nitrogen to inorganic sulfate is a closer index of the food metabolized than the total nitrogen-sulfur ratio though of course there is a strong parallelism. On the other hand, this means that one is forced to conclude that the protein of the diet is handled in a normal fashion so far as the portion that is excreted is concerned.

Can any further information be obtained from the other sulfur or nitrogen fractions? The neutral sulfur seemed to represent a slightly larger fraction of the total sulfur in the patient with cirrhosis and a considerably larger percentage in the patient with nephrosis, being more than double the normal on the average. The significance of this increase in neutral sulfur is not clear, though variations in this fraction are usually referred to changes in the intermediary protein metabolism. Similar considerations apply to the ethereal sulfates, except that in the patient with nephrosis a striking effect was produced by the administration of urea in a lowering of this fraction. This is difficult to explain, as this fraction is alleged to arise from intestinal putrefaction and to be an index thereof. How urea, an indifferent, completely absorbed substance, can effect the excretion of ethereal sulfate is difficult to imagine unless one is dealing with some sulfur linkage similar to that described by Johnson¹³ and conjugated in these patients to ethereal sulfates. As these processes are concerned with the liver, it seems desirable to search further for pathologic processes in this organ in these patients and to recall that the patient with cirrhosis and the one with nephrosis both exhibited positive nitrogen and sulfur balances amounting to retention.

¹³ Johnson, T. B., cited by Kahn, M., and Goodridge, F. G. Sulfur Metabolism. A Review of the Literature, Philadelphia: Lea & Febiger, 1926, chap. 35.

As far as we can gather from these experiments, it seems fairly possible to conclude that there are underlying metabolic disturbances affecting particularly the sulfur-rich moiety of the protein molecule in patients with nephrosis and that, as there are certain gross similarities between patients with cirrhosis and those with nephrosis in regard to the nitrogen and sulfur balances, it is desirable to search further for disturbances of the hepatic function in nephrotic patients. That the retention of nitrogen merely compensates for the depletion of serum protein is not tenable, as there is retention beyond the protein nitrogen lost without causing a change in the level of the serum protein. The thought that such retention went to replacing the tissue proteins that possibly had been called on in our patient with nephrosis is untenable, since there was no corresponding gain in weight. The avidity with which such patients retain sulfur suggests that one may be dealing with a primary derangement of the metabolism of the sulfur-rich moiety of the protein molecule or possibly with the intermediary sulfur metabolism. There is slight evidence that the kidney plays a rôle in the metabolism of cystine, and it may be that this mechanism is involved in Bright's disease. On the other hand, the patient with cirrhosis showed retention of sulfur and nitrogen in equal proportions, and it is therefore reasonable to suppose that while part of the mechanism of the retention of sulfur and nitrogen in these two cases may be identical, there is some additional factor involved in nephrosis.

In contrast to the retention of sulfur discussed in the preceding paragraph, how is one to explain the negative sulfur balance in the patient with glomerulonephritis? If nephrosis always occurred as an incident in the course of glomerulonephritis, one might assume that the opposite reactions in the two conditions complement or follow each other. While the effort to retain sulfur appears to extend to the protein of nephrotic patients, the converse cannot be definitely demonstrated of the protein in the patients with glomerulonephritis. It seems to us that the two findings may be manifestations of entirely different mechanisms. It is impossible with the present evidence to explain the findings. Their tabulation in summary will indicate possibly the future attack on this phase of Bright's disease.

Since this is the final report of this series of experiments, it seems desirable to include in the summary all the results obtained. We conclude that the evidence of abnormal protein metabolism suggests that further study of this problem may ultimately yield fruitful practical data.

SUMMARY

Patients with the nephrosis syndrome retain nitrogen and sulfur.¹ They remain in positive nitrogen and sulfur balance, but a larger proportion of sulfur than of nitrogen is retained.

This positive balance is not due to the edema per se,¹⁴ to excess dietary sulfur¹⁵ or to retention in the blood. It extends to crystalline urea.³

The neutral sulfur fraction of the urine is increased in nephrosis.

Patients with glomerulonephritis are in negative sulfur balance,² but the nitrogen balance is even except for the nitrogen contained in the protein excreted.

The protein excreted in the urine during the nephrosis syndrome is low in sulfur and is not serum albumin.¹⁰

A patient with cirrhosis of the liver showed a positive sulfur and nitrogen balance but in equal proportions.

CONCLUSION

In the various forms of Bright's disease variations in the excretion of nitrogen and sulfur have been demonstrated which indicate that there are changes in the protein metabolism affecting probably the sulfur-rich moiety of the protein molecule. Such changes may be a fundamental factor in these conditions.

14 Grabfield, G. P., Driscoll, M., and Gray, M. G. Nitrogen and Sulphur Metabolism in Bright's Disease. V. Metabolic Study of a Patient with Edema of Unknown Origin, *Arch. Int. Med.* **54**: 764 (Nov.) 1934.

15 Grabfield, G. P., and Adams, L. G. Nitrogen and Sulphur Metabolism in Bright's Disease. VI. Effect of Diets Low in Sulphur on the Excretion of Sulphur, *Arch. Int. Med.* **55**: 360 (March) 1935.

ROENTGENOGRAPHIC STUDY OF ORTHOSTATIC ALBUMINURIA BY MEANS OF INJECTIONS OF DIODRAST

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That the pathogenesis of orthostatic albuminuria is poorly understood is attested by recent reviews¹ The name orthostatic albuminuria is derived from a clinical symptom—the presence of an increased amount of protein in the urine while the subject is erect and its fall to a normal level (clinical absence) when he is supine The object of this paper is to indicate the importance of determining the anatomic basis for this symptom by means of roentgenograms made after the injection of diodrast The experience of my colleagues and myself in the first five cases in which this method was applied seems to indicate that orthostatic albuminuria arises from diverse anatomic anomalies and cannot be regarded as a distinct entity

Two general theories may be considered seriously, the circulatory and the mechanical theory The circulatory theory explains the anomaly on the following bases First (*a*) in orthostatic albuminuria the amount of protein excreted varies inversely with the pulse pressure,² (*b*) in animal experiments a decrease in the pulse pressure leads to a diminution of the renal secretion and (rarely) albuminuria³ and (*c*) in normal human subjects the erect posture results in a diminution of the renal secretion⁴ Furthermore, (*a*) there are increases in the concen-

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1 (*a*) Medes, G, and Neemes, M Orthostatic Proteinuria, in Berglund, H, and Medes, G The Kidney in Health and Disease, Philadelphia, Lea & Febiger, 1935, p 462 (*b*) Fishberg, A M Hypertension and Nephritis, ed 2, Philadelphia, Lea & Febiger, 1931, p 257 (*c*) Volhard, F Die doppelseitigen haematogenen Nierenerkrankungen, in von Bergmann, E, and Staehelin, R Handbuch der inneren Medizin, Berlin, Julius Springer, 1931, vol 6, p 832 (*d*) Hartwich, A Die gutartigen Albuminurien, *Ergebn d inn Med u Kinderh* **38** 44, 1930

2 Erlanger, J, and Hooker, D R An Experimental Study of Blood-Pressure and of Pulse Pressure in Man, *Johns Hopkins Hosp Rep* **12** 145, 1904

3 Gesell, R A On the Relation of Pulse Pressure to Renal Secretion, *Am J Physiol* **32** 70 (May) 1913

4 White, H L, Rosen, I T, Fischer, S S, and Wood, G H The Influence of Posture on Renal Activity, *Am J Physiol* **178** 185 (Sept) 1926

tiation of protein in the blood (13 per cent) and in the colloidal osmotic pressure (23 per cent) on standing,⁵ (b) the glomerular filtration rate varies inversely with the colloidal osmotic pressure,⁶ and (c) direct observation of glomerular urine of frogs has shown that albuminuria accompanies very slow rates of filtration.⁷ Objections to the circulatory theory are that not all subjects with orthostatic albuminuria have a low pulse pressure on standing erect,⁸ that patients with aortic stenosis or a low pulse pressure from other causes do not necessarily exhibit albuminuria, that orthostatic albuminuria ordinarily appears before the changes in the osmotic pressure occur and that various investigators have found unilateral albuminuria (usually on the left) on ureteral catheterization.

The mechanical theory explains orthostatic albuminuria (a) as related to venous compression by lordosis of the lumbar portion of the spine⁹ (but lordosis may be present unassociated with orthostatic albuminuria¹⁰) or, more definitely, (b) as due to compression of the left renal vein by the vertebral column and aorta,¹¹ the superior mesenteric artery¹² or the angle formed by these two vessels.¹³

Attractive as the unilateral (left) mechanical theory is on anatomic grounds, the direct evidence in its favor is far from convincing. In six cases of orthostatic albuminuria Sonne¹¹ passed ureteral catheters; none of the patients showed albumin in the urine from the right side, one showed total anuria, three others showed anuria on the left alone and two showed albumin in the urine from the left kidney. Haitwisch¹⁴ found bilateral albuminuria in two subjects and albuminuria on the left

5 Youmans, J. B., Wells, H. S., Donley, D., Miller, D. G., and Frank, H. The Effect of Posture (Standing) on the Serum Protein Concentration and Colloidal Osmotic Pressure of Blood from the Foot in Relation to the Formation of Edema, *J. Clin. Investigation* **13** 447 (May) 1934.

6 Ni, T., and Rehberg, P. B. On the Influence of Posture on Kidney Function, *J. Physiol.* **71** 331 (March 23) 1931.

7 Wearn, J. T., and Richards, A. N. Observations on the Composition of Glomerular Urine, with Particular Reference to the Problem of Reabsorption in the Renal Tubules, *Am. J. Physiol.* **71** 209 (Dec.) 1924.

8 Bass, M. H., and Wessler, H. A Study of the Blood-Pressure in Children Showing Orthostatic Albuminuria, *Arch. Int. Med.* **13** 39 (Jan.) 1914.

9 Jehle, L. *Die Albuminurie*, Berlin, Julius Springer, 1914.

10 Lewison, M., Freilich, E. B., and Ragins, O. B. Lordosis as a Cause of Postural Albuminuria, *Arch. Int. Med.* **42** 440 (Sept.) 1928.

11 Sonne, C. Beitrag zur Aetiologie der lordotischen orthostatischen Albuminurie, *Ztschr. f. klin. Med.* **90** 1, 1920.

12 Rieser, W., and Rieser, S. L. The Etiology of Orthostatic Albuminuria, *J. A. M. A.* **78** 644 (March 4) 1922.

13 Kristenson, A. Beitrag zur Kenntnis der Pathogenese der orthostatischen Albuminurie und der Varikozele, *Upsala Lakaref. förh.* **31** 641, 1926.

in only one Ehrmann¹⁴ studied a subject with edema of the left leg, on catheterization urine from the right kidney was albumin free, and there was anuria on the left Russell¹⁵ saw two patients (neither catheterized) with edema of the left leg, he concluded from anatomic studies that the left kidney was congested, causing the albuminuria Vorpahl¹⁶ had a patient with marked scoliosis, lumbar convexity on the left and albuminuria When the scoliosis was temporarily corrected, the albuminuria ceased Ureteral catheterization on two occasions yielded normal urine from the left and albuminous urine from the right Even more indirectly, Rieser and Rieser¹² were able to diminish orthostatic albuminuria in two viscerotomic women (one of whom had undergone excision of the right kidney) by a supportive abdominal corset and drew attention to the aorta-mesenteric artery "pincers"

Kristenson,¹³ in an exhaustive study, noted a thrombotic process in the cephalad wall of the left renal vein at the crossing of the superior mesenteric artery in 25 per cent of one hundred and twenty-one subjects at necropsy The process was evenly distributed among males and females and was not noted in subjects less than 8 years of age In five instances the left renal vein ran behind the aorta—the wall of one of these veins was the site of a similar but larger thrombotic process where it lay under the aorta In addition to his necropsy studies, Kristenson (considering the connection anatomically between the left renal and the spermatic vein) examined eight hundred and thirty-six soldiers in the kneeling position (forced lordosis) for orthostatic albuminuria and varicocele on the left side 26 per cent had a potential varicocele on the left side, 22 per cent had albuminuria and 8 per cent had both Fifty per cent of those with marked varicocele had orthostatic albuminuria

METHODS

Five young men exhibiting orthostatic albuminuria but otherwise not selected were studied in recumbent and erect postures roentgenographically after the injection of diodrast Four of the subjects entered the hospital for the investigation, and the fifth one was studied as an outpatient

The roentgenographic observations were carried out as follows After a night's rest in bed each subject was taken to the roentgenologic department in a supine position, diodrast was injected and roentgenograms were taken without permitting a change in the subject's position The subject then stood up and walked about After one and one-half hours diodrast was again injected while the subject was erect, and roentgenographic examinations were made In the first trial of one subject, L S, events were followed fluoroscopically in both posi-

14 Ehrmann, R Orthostatische Albuminurie mit chronischem Oedem des linken Beines, Berl klin Wchnschr 48 496, 1911

15 Russell, J W Two Cases of Unilateral Edema with Albuminuria, Lancet 2 925 (Oct 27) 1923

16 Vorpahl, K Ueber einseitige orthostatische Albuminurie, Berl klin Wchnschr 47 827, 1910

tions and confirmed by four roentgenograms. One week later he was studied in the erect position alone by means of ten roentgenograms taken within thirteen minutes after completion of the injection of diodrast. The other four subjects were studied on one occasion each, eight roentgenograms were taken in each position within from eight to twenty minutes after the injection of diodrast. Since J C could not enter the hospital, roentgenograms were first made while he was in the erect posture. After he had been lying down for two hours he was examined in the supine position.

RESULTS

With L S supine under the fluoroscope, diodrast was seen to appear nine minutes after its injection, in good concentration, simultaneously on the two sides (confirmed by two roentgenograms). With the subject erect diodrast was first seen in the right kidney ten minutes after the second injection, but it was

*The Areas of the Shadows of the Kidneys of Five Subjects with Orthostatic Albuminuria**

	Recumbent Position	Erect Position	Change on Standing
L S			
Right	53	53	± 0
Left	51	62	+11
K B			
Right	53.5 ± 1.2	50 ± 0.9	-3.5 ± 1.5
Left	61.5 ± 0.6	67.8 ± 1.1	$+6.3 \pm 1.2$
O B			
Right	101.4 ± 0.8	96 ± 0.9	-5.4 ± 1.2
Left	35 ± 1.1	30.5 ± 0.5	-4.5 ± 1.2
J P			
Right	59 ± 0.6	85 ± 0.5	$+26 \pm 0.8$
Left	80 ± 1.0	85 ± 0.8	$+5 \pm 1.3$
J C†			
Right	65 ± 0.8	74 ± 0.5	$+9 \pm 0.9$
Left	74 ± 0.6	70 ± 0.4	-4 ± 0.7

* The areas are given in square centimeters, with probable errors.

† This subject was ambulatory. The studies with the subject erect were made first and then those with the subject recumbent.

not seen for twenty minutes on the left. Roentgenograms at that time showed good concentration on the right and a very small amount of the contrast medium on the left. The subject then reclined and diodrast reappeared on the left (seen under the fluoroscope) in two minutes. In the second trial on L S made one week later, in the erect position only, diodrast was seen in the first roentgenogram (one minute after injection) in the right kidney only. It was not seen until a sixth roentgenogram (six minutes later) on the left, in succeeding roentgenograms it was seen in small amounts on the left side, but there was never as much as on the right. The right kidney was seen to contain a constant amount of well concentrated diodrast throughout the ten roentgenograms, outlining the pelvis and most of the calices. On the left only a few spots of diodrast were ever seen.

With K B supine, diodrast appeared faintly in one minute but in good concentration three minutes after the injection, the same on the two sides, outlining a normal pelvis and calices. With the subject erect, diodrast appeared on both sides within two minutes after injection, but while it quickly reached a heavy concentration on the right (though not as concentrated as when the subject was supine), it was never well seen on the left.

O B was found to have a very small left kidney and a large right one. Diodrast appeared bilaterally in three minutes when he was supine and in seven minutes when he was erect. The concentration was about equal bilaterally and was not appreciably affected by the changes in posture.

J P was found to have reduplication of the ureter and renal pelvis on the left and a very mobile right kidney. When he was supine, diodrast appeared on both sides in two minutes, when he was erect, in ten minutes. The concentration was about equal bilaterally but was more dense with the subject supine (although two roentgenograms taken in the latter position failed to show the upper part of the pelvis on the left side).

As J C was unable to enter the hospital, the first set of roentgenograms was made while he stood and the second set after he had been supine for two hours. Diodrast appeared promptly on each side regardless of the subject's posture,

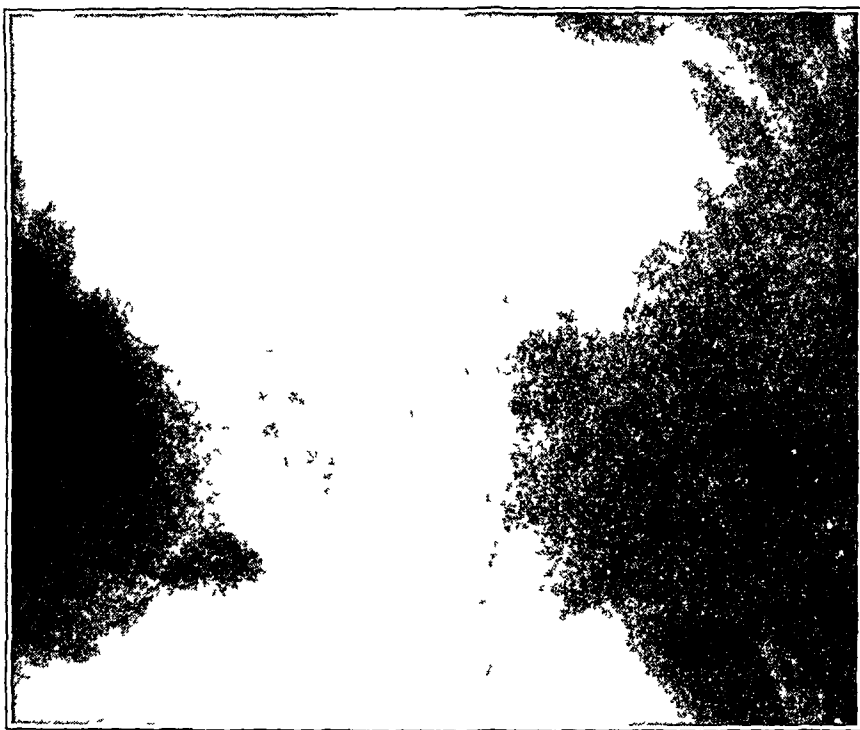


Fig 1—Roentgenogram of L S in the erect position. In figures 1 to 5 the patient's left side is to the observer's right.

likewise, posture did not materially affect the final concentration, which was always good. While the subject was standing, the upper outer pole of the left kidney appeared to be somewhat flattened; no other abnormalities were observed.

Assumption of an upright posture was associated with the following descents in the position of the renal shadow: L S—right 1 cm and left 1 cm, K B—right 0 and left 2 cm, O B—right 1 cm and left 1.5 cm, J P—right 5.5 cm and left 1 cm, J C—right 0 and left 1.5 cm.

The shadows of the kidneys were outlined on suitably clear roentgenograms, and their areas were measured with a planimeter. In L S the outlines were measurable in only one pair of roentgenograms, but in the other subjects the outlines were distinct in most of the sixteen roentgenograms.

The accompanying table presents the results of the measurements, while figures 1 to 5 show the appearance of the roentgenograms.

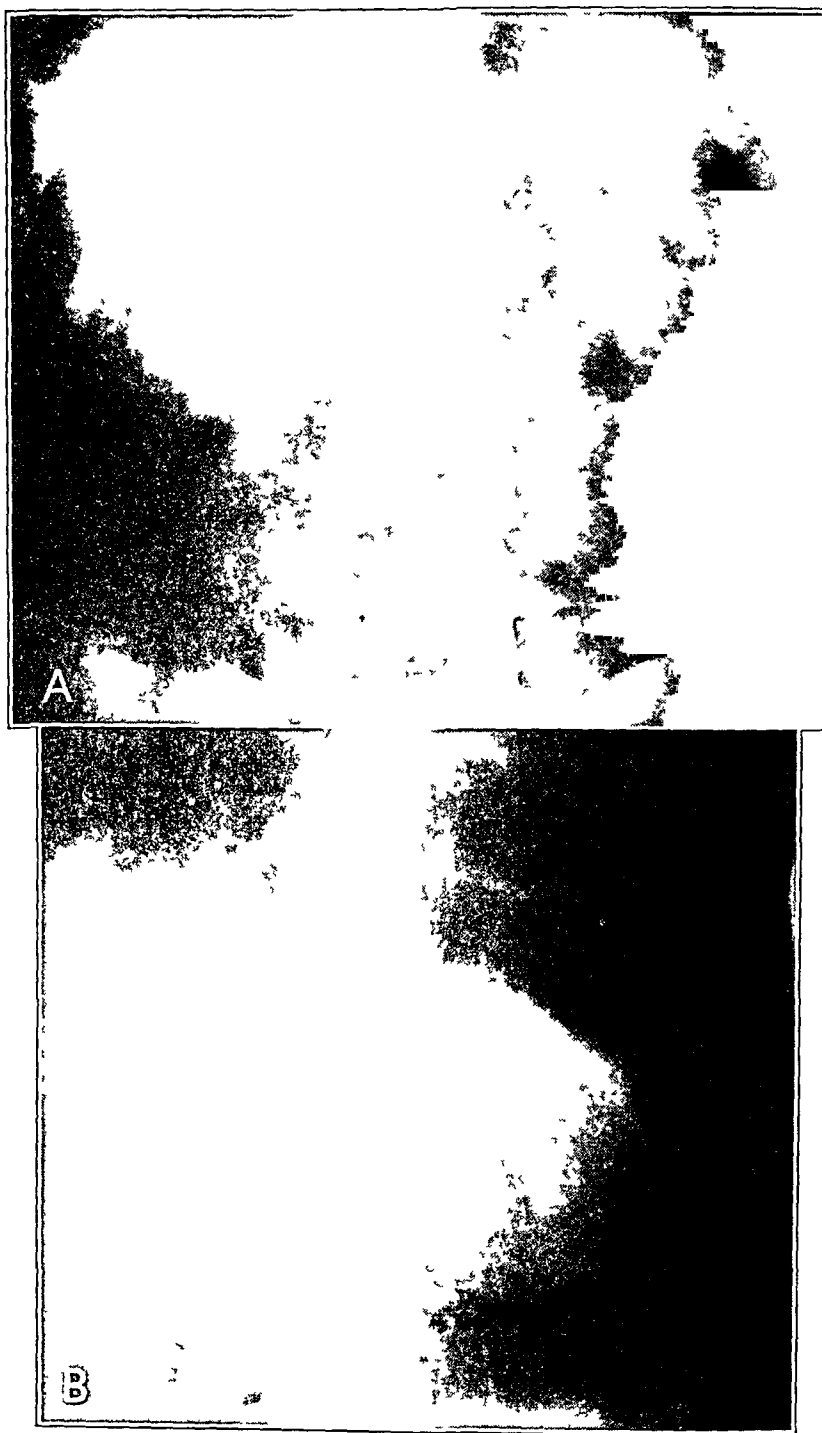


Fig 2—Roentgenograms of K B in the supine (*A*) and the erect (*B*) position

The measurements of the areas showed statistically significant changes with changes in posture in every subject. There are two possible interpretations of the changes, (a) they were due to rotation of the renal axis with respect to the x-ray beam, or (b) they may have had

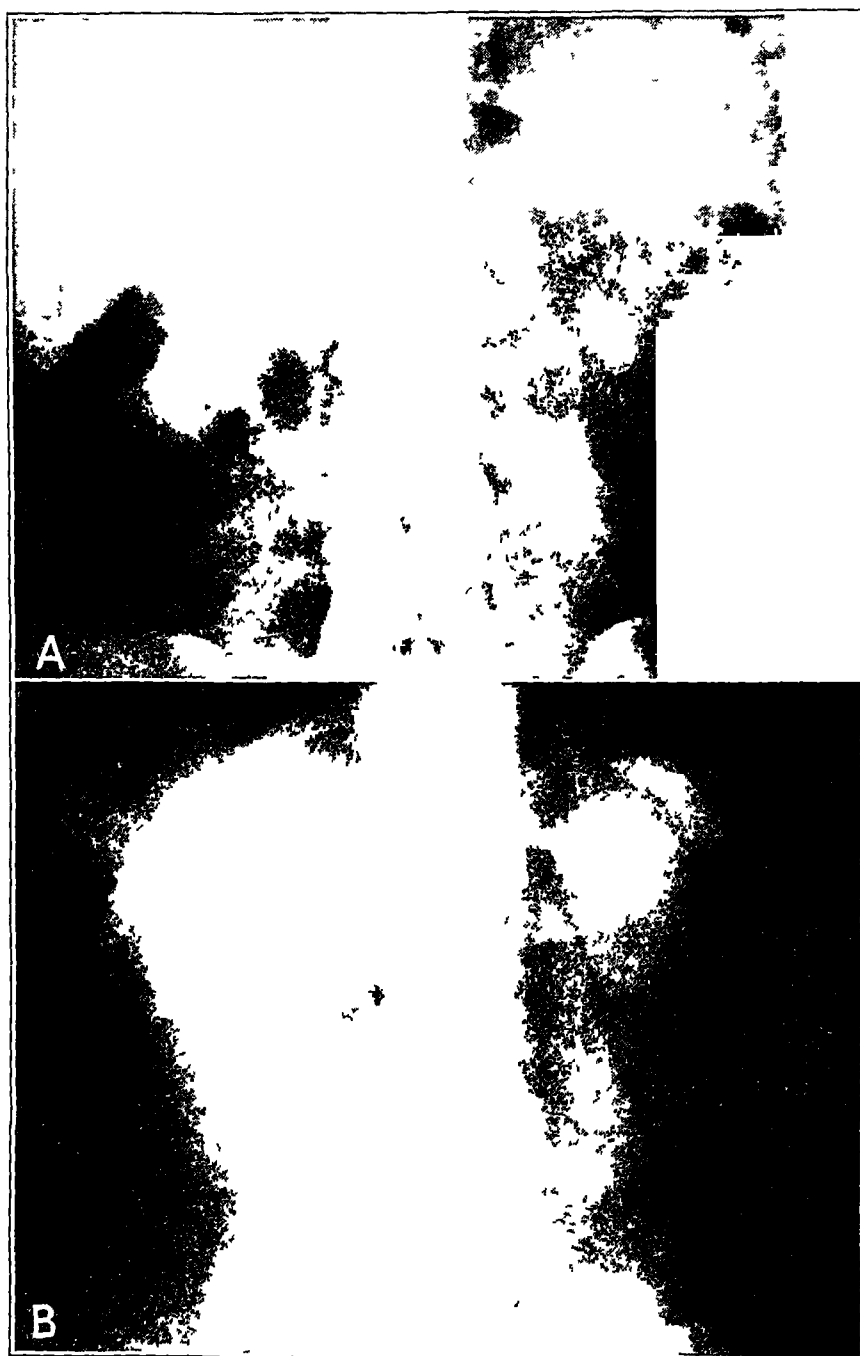


Fig 3—Roentgenograms of O B in the supine (A) and the erect (B) position

physiologic significance, i e, a decreased area when the subject stood may have been the result of a low pulse pressure, while an increased area may have been brought about by venous stasis in spite of the lower perfusion pressure

In an effort to interpret the changes in area correctly, further studies at other times were made of J P and J C. A single roentgenogram of J P standing gave an area of 90 sq cm for each kidney. He was then placed in the supine position, and another roentgenogram was made within thirty seconds. The area

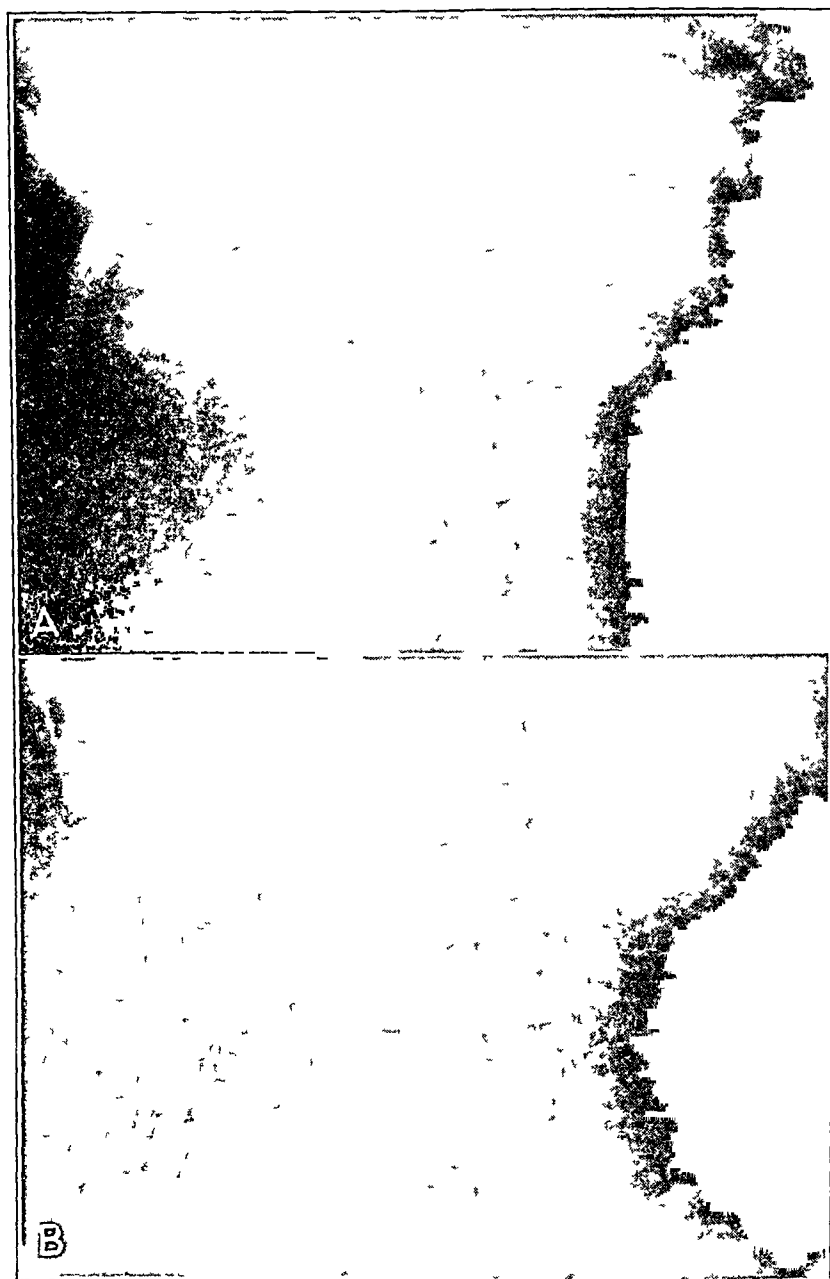


Fig 4—Roentgenograms of J P in the supine (A) and the erect (B) position

of the right kidney was then 59 sq cm and that of the left 88. In the case of J P, therefore, rotation of the renal axis was sufficient to explain the changes observed in the area of the shadow of the right kidney, while changes on the left side may have had physiologic significance. For J C roentgenograms were taken three and five minutes after he reclined, following a series of six roent-

genograms taken while he was in the erect position. The area of the left kidney failed to change appreciably, the mean area of the right kidney in the six films taken while the subject was erect was 74 ± 0.5 sq cm, after the subject had been supine for three minutes the area was 73 sq cm, and after five minutes it was



Fig 5—Roentgenograms of J C in the supine (A) and the erect (B) position

68 sq cm. Conversely, roentgenograms were taken three and five minutes after he had stood up, following the taking of a series of six roentgenograms while he was in the supine position. Again the shadow of the left kidney did not change, the mean area of the shadows of the right kidney in six roentgenograms taken with the subject supine was 65 ± 0.8 sq cm, after the subject had been erect

for three minutes it was 66 sq cm, and after five minutes it was 68 sq cm. These results suggest, but do not prove, that in J C at least the increase in the area of the shadow of the right kidney when he stood was due to actual engorgement of the kidney because of venous stasis and was not due to rotation of the axis.

COMMENT

As far as is known, diodrast has not been used previously in the roentgenographic study of orthostatic albuminuria, even though it has been used as a test of function¹⁷ (see also the references cited by Landis and his colleagues¹⁸) and its clearance has been studied.¹⁹ The only use of roentgenograms in this connection seems to have been that depicted by Young and Waters,²⁰ interpreted as showing transitory albuminuria as the result of the crossing of aberrant blood vessels over the ureter.

The results obtained with diodrast may be conveniently grouped into three categories. First, in two subjects (L S and K B) the left kidney excreted diodrast very poorly, and its shadow became larger with the subject erect. Secondly, in two other subjects (O B and J P) there were gross anatomic anomalies of the kidneys, but posture did not affect the excretion of diodrast unilaterally to any degree. Finally, no significant abnormalities were disclosed by diodrast in J C.

An interpretation of the changes in the area of the renal shadows is difficult. By a special technic we were able to show that the large variation in the right kidney of J P was due to rotation, the results in the case of J C suggested that the changes were related to congestion and not to rotation. Unfortunately, this technic was not in use while L S and K B were being studied, it would be excellent additional evidence in favor of the mechanical theory if it could be shown that such increases in the area of the left kidney as they exhibited were not caused by rotation of the renal axis.

To summarize, four of five subjects showed definite abnormalities on roentgenographic examination, two showing totally unexpected gross renal defects, presumably congenital in origin. The unilateral (left)

17 Braasch, W F, and Emmett, J L. Excretory Urography as a Test of Renal Function, *J Urol* **35** 630 (June) 1936.

18 Landis, E M, Elsom, K A, Bott, P A, and Shiels, E H. Simultaneous Plasma Clearances of Creatinine and Certain Organic Compounds of Iodine in Relation to Human Kidney Function, *J Clin Investigation* **15** 397 (July) 1936.

19 Elsom, K A, Bott, P A, and Shiels, E H. On the Excretion of Skiodan, Diodrast and Hippuran by the Dog, *Am J Physiol* **115** 548 (May) 1936. Landis, Elsom, Bott and Shiels¹⁸.

20 Young, H H, and Waters, C A. *Urological Roentgenology*, New York, Paul B Hoeber, Inc, 1928, p 132, figs 129-130.

abnormalities in the other two subjects fit in well with the mechanical theory of stasis of the left renal vein, presumably due to compression of the vein between the superior mesenteric artery and the aorta

It was not possible to catheterize the subjects. In the absence of such direct evidence, one might conclude that the proteinuria was on the left only in L S and K B, speculation regarding the other subjects is fruitless in the face of the hypoplastic left and hypertrophied right kidney of O B, the reduplicated left ureter and pelvis and the mobile right kidney of J P and the absence of definite findings in J C

SUMMARY AND CONCLUSIONS

Five unselected subjects with orthostatic albuminuria were studied roentgenographically after the injection of diodrast

In two subjects when they were in the supine position diodrast appeared normally in both kidneys, when they were erect it appeared in low concentration in the left kidney, which became larger. In three other subjects posture did not significantly alter the excretion of diodrast unilaterally. One of these subjects had a very small left kidney and a large right one, and a second had a reduplicated left ureter and renal pelvis and a mobile right kidney. No abnormalities were found in the third subject

Much helpful advice and cooperation were received from the members of the roentgenologic department, especially from Dr Edward Leef

THE RENAL LESION IN ORTHOSTATIC ALBUMINURIA

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The results reported in a foregoing paper¹ show that because of the diversity of anatomic renal defects orthostatic albuminuria cannot be regarded as a distinct disease entity. Even the purely clinical definition of orthostatic albuminuria shows a lack of precision. It is incorrect to state that orthostatic albuminuria is a condition characterized by the presence of albumin in the urine while the subject is erect and by the absence of albumin in the urine while he is supine, because albumin (protein) is always present under all conditions. What is really meant is that more albumin is present under certain circumstances than under others. Since this is the case, quantitative methods are essential.

The same five subjects with orthostatic albuminuria who were studied roentgenographically after the injection of diodrast, reported on in the foregoing paper,¹ were further investigated by means of the Addis urea ratio, the Rehberg (creatinine) glomerular filtration rate and the Addis count of the urinary sediment.

It has been stated that tests of the renal function show no impairment in cases of true orthostatic albuminuria, but these tests are usually for the concentration of urea in the blood or the excretion of phenol-sulfonphthalein, either of which may fail to show even a gross (50 per cent) reduction of function.²

Medes and Neemes³ have determined the rate of glomerular filtration by the creatinine method for normal subjects and for those with orthostatic albuminuria. Their results showed 171 ± 4 cc, 158 ± 5 cc and 155 ± 7 cc per minute for normal subjects, subjects with mild and subjects with severe "lordotic proteinuria," respectively, during thirty minutes of recumbency. The rates were 167 ± 5 cc, 153 ± 7 cc and 102 ± 9 cc, respectively, for subjects in the lordotic position during

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1 Rytand, D A. Roentgenographic Study of Orthostatic Albuminuria by Means of Injections of Diodrast, *Arch Int Med*, this issue, p 837

2 MacKay, E M, and Rytand, D A. Significance of Phenolsulphonphthalein Test of Renal Function, *Arch Int Med* 60 131 (Jan) 1935

3 Medes, G, and Neemes, M. Orthostatic Proteinuria, in Berglund, H, and Medes, G. *The Kidney in Health and Disease*, Philadelphia, Lea & Febiger, 1935, p 462

twenty minutes of standing. That is, the rate of glomerular filtration fell only in those with the more severe orthostatic renal lesions. It is unfortunate that the experimental periods were not longer. While White and his associates⁴ found that renal secretion was diminished in normal subjects in the erect position, Van Slyke and his associates⁵ found no change in the urea clearance. The latter observers, however, found that in three of twelve nephritic patients with less than 50 per cent of normal clearance, standing (walking) further reduced the standard clearance to from 44 to 67 per cent of its value when the patient was at rest in bed.

METHODS

For the same subjects with orthostatic albuminuria for whom diodrast studies were made and within one or two days of the time of those studies, the Addis urea ratio⁶ and the Rehberg creatinine clearance⁷ were determined simultaneously over four consecutive hours. The subjects were recumbent for twelve hours prior to and during the first two hours and standing during the second two hours. They were fasting except for 20 Gm of urea and 5 Gm of creatinine three hours and one and one-half hours, respectively, before the collection of urine was started. Brisk diuresis was obtained by giving a large amount of water. One subject, J. C., being ambulatory, was erect during the first two hours and supine the succeeding two hours.

Repeated Addis counts⁸ of the urinary sediment were made on specimens for from one to eight hours obtained from each of the subjects (fifty-six in five days) for L. S., sixteen in four days for K. B., twelve in four days for O. B., twelve in five days for J. P. and eight in four days for J. C.). Conditions were arranged so that separate specimens were obtained with the subject standing quietly, at ordinary activity, exercising violently (three subjects only) or at rest in bed.

RESULTS

Function Tests—Table 1 shows that the results of the function tests paralleled closely those obtained roentgenographically after the injection of diodrast. In L. S. and K. B. (in whom it was noted that while they stood diodrast was excreted poorly by the left kidney, which became

4 White, H. L., Rosen, I. T., Fischer, S. S., and Wood, G. H. The Influence of Posture on Renal Activity, *Am J Physiol* **178** 185 (Sept.) 1926.

5 Van Slyke, D. D., Alving, A., and Rose, W. C. Studies of Urea Excretion. VII The Effects of Posture and Exercise on Urea Excretion, *J Clin Investigation* **11** 1053 (Sept.) 1932.

6 Addis, T., and Watanabe, C. K. A Method for the Measurement of the Urea-Excreting Function of the Kidney, *J Biol Chem* **28** 251 (Dec.) 1916.

7 Rehberg, P. B. Studies on Kidney Function. I The Rate of Filtration and Reabsorption in the Human Kidney, *Biochem J* **20** 447 (April 26) 1926, II The Excretion of Urea and Chlorine Analyzed According to a Modified Filtration-Reabsorption Theory, *ibid* **20** 461, 1926.

8 Addis, T. A Clinical Classification of Bright's Disease, *J A M A* **85** 163 (July 18) 1925.

larger) the renal function during the second hour of standing quietly was only one-half as great as the mean function while the subject was supine. On the other hand, in O B and J P (who had gross anatomic anomalies but who showed no postural change in the excretion of diodrast) posture did not affect the renal function. Finally, in J C (in whom there were no definite findings roentgenographically) the renal function while he was in the erect position was 81 per cent of that while he was supine.

The rates of proteinuria were determined during the clearance studies. In O B and J P the rates were too low to be measured. L S excreted protein at the rate of 6 mg per hour while supine and

TABLE 1—*Addis Urea Ratio and Glomerular Filtration Rate (Creatinine) in Five Subjects with Orthostatic Albuminuria in Recumbent and Erect Positions*

Position	Hour	L S		K B		O B		J P		J C*	
		Addis Ratio, % of Normal	Filtration Rate, Cc per Min	Addis Ratio, % of Normal	Filtration Rate, Cc per Min	Addis Ratio, % of Normal	Filtration Rate, Cc per Min	Addis Ratio, % of Normal	Filtration Rate, Cc per Min	Addis Ratio, % of Normal	Filtration Rate, Cc per Min
Recumbent	1	59	101	100	138	76	149	78†	253	88	210
	2	63	107	107	112	78	169	122	326	91	205
	Mean	61	104	103	125	77	159	122	290	90	207
Erect	3	60	78	70	114	83	149	141	344	81	187
	4	38	56	42	54	85	120	109	279	70	176
Last hour erect in percentage of value when recumbent		62	54	41	43	110	75	89	96	78	85
Mean, percentage		58		42		92		92		81	

* The subject was ambulatory. The studies with the subject erect were made before those when he was recumbent.

† Omitted in the calculations because of a lag in reaching the peak of urea excreting efficiency.

269 mg while erect, K B excreted 4 mg per hour while supine and 58 mg while erect, and J C excreted 140 mg per hour while supine and 225 mg while erect.

Renal Lesions—In the two instances in which necropsy reports were obtained for patients with undoubted orthostatic albuminuria who died as a result of some other disorder,⁹ no significant renal lesions were discovered. Little has been written about the urinary sediment, other than that oxalate crystals, a few red blood cells and "hyaline and even granular casts in small numbers"¹⁰ may be found. As a result, one is

9 Heubner, O. Die chronischen Albuminurien im Kindesalter, *Ergebn d inn Med u Kinderh* 2:567, 1908. Holst, P. F. Orthostatic Albuminuria and Its Relation to Nephritis, *Norsk mag f lægevidensk* 13:1377, 1915. *abstr*, *J A M A* 65:2206 (Dec 18) 1915.

10 Fishberg, A. M. Hypertension and Nephritis, ed 2, Philadelphia, Lea & Febiger, 1931, p 257.

prone to think of orthostatic *albuminuria* rather than of an orthostatic renal lesion

Table 2 gives the minimum and maximum intensities of the renal lesions as determined by the Addis sediment count with the subject in bed and standing quietly, respectively. The usual findings with the subject erect approached the maximum given in the table.

Data were obtained for three subjects during violent exercise (running). L. S. excreted only 19 mg of protein, 21,400 casts, 8,700 red blood cells and 351,000 epithelial cells per hour. J. P. excreted only 166 mg of protein, 29,200 red blood cells and 292,000 epithelial cells but as many as 175,000 casts per hour. J. C. excreted only 155 mg of protein and 38,000 red blood cells but as many as 171,000 casts and 152,000 epithelial cells per hour. In brief, the intensities of the renal lesions were less during violent exercise than when the subject stood quietly (compare with table 2).

TABLE 2—Rates of Excretion of Protein and Formed Elements in Five Subjects with Orthostatic Albuminuria*

Rates of Excretion per Hour†	L. S.	K. B.	O. B.	J. P.	J. C.
Protein, mg	4 690	2 132	5 69	3 263	12 406
Casts	0 90,400 90% granular 10% hyaline	0 46,600 100% granular	0 9,200 80% granular 20% hyaline	0 16,700 100% granular	0 16,700 100% granular
Red blood cells	0 292,000	0 18,700	0 9,200	0 41,700	4,400 61,200
White and epithelial cells‡	15,000 6,250,000	21,500 933,000	45,000 83,400	11,700 583,000	26,200 92,000

* The upper rows of figures give the minimal findings with the subject in bed. The lower rows of figures give the composite maximal findings with the subjects up and about.

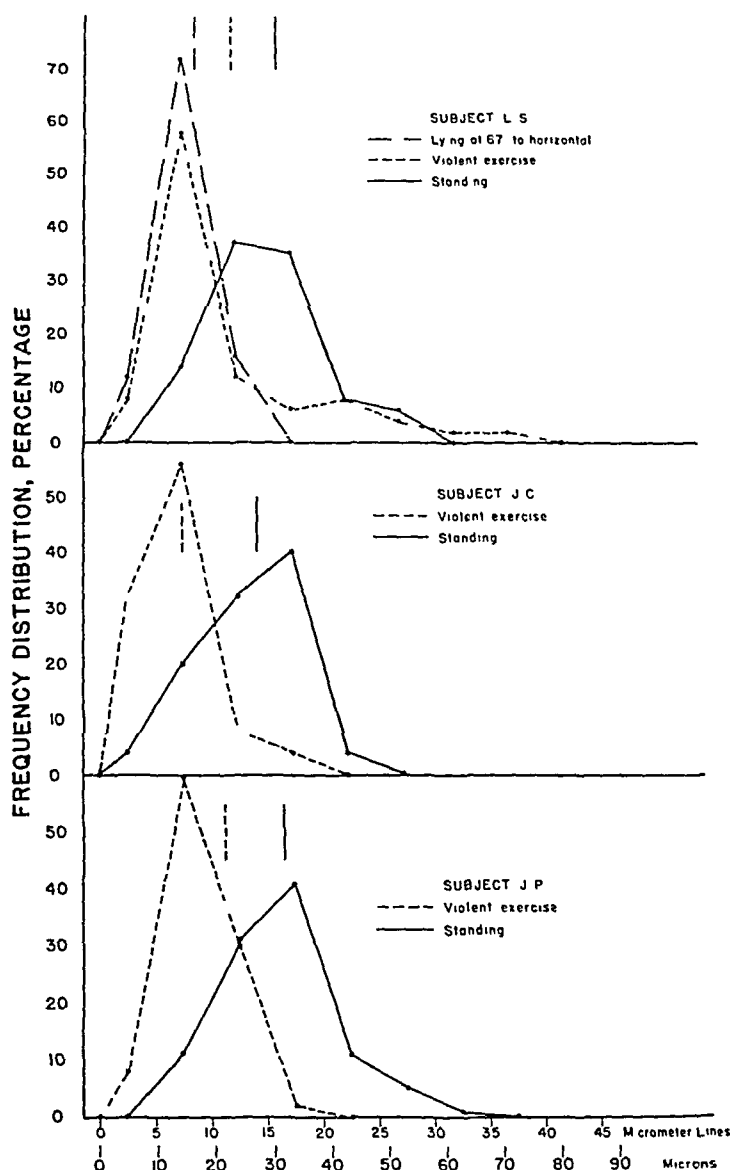
† The upper limits of normal are approximately 8 mg of protein, 400 casts, 80,000 red blood cells and 80,000 white and epithelial cells per hour.

‡ Almost all were renal tubular epithelial cells.

Congo red was injected intravenously into L. S. at a time when the urine contained 532 mg of protein per hour, it definitely colored the urine pink and under the microscope could be seen staining the casts. Hartwich¹¹ previously reported a similar finding.

Such data for the sediment as are given in table 2 (including the healing of the process under favorable conditions) and the escape of congo red are similar to those encountered in cases of any degenerative renal lesion, the outstanding feature here being the extreme rapidity of the degeneration and regeneration. Observations on L. S. indicated that urinary evidences of renal degeneration (protein, casts and tubular epithelial cells) were much less pronounced about one hour after the supine position had been assumed. The onset of the degeneration usually

began within one hour after the subject stood upright but sometimes did not appear until the second hour. It is generally accepted also that renal degeneration may go on to a diminution of function, as had apparently occurred in L. S. The speed of regeneration is such that at necropsy performed on a subject with orthostatic albuminuria who had



Frequency distribution of the casts according to width in three subjects with orthostatic albuminuria

been ill in bed for some time before death one might well expect to observe no abnormality on histologic examination of the kidneys

The width of the casts in the sediment was measured for L. S., J. P. and J. C., for whom both roentgenographic and clearance studies suggested different pathogenic mechanisms of the renal lesions. Figure 1 presents the frequency distributions of the casts by width

In urine collected while the subject was standing quietly, the mean width (on samples of from 100 to 250 casts) was 30.6 microns for L. S., 31.1 microns for J. P. and 26.9 microns for J. C. In urine obtained shortly after violent exercise the mean width of the casts was only 22.8 microns for L. S., 21.2 microns for J. P., and 14.1 microns for J. C. For L. S., reclining at an angle of 67 degrees to the horizontal for several hours, the mean width of the casts was 16.6 microns. The width of the casts excreted with the subject standing quietly approached that of the broad casts seen in cases of renal failure,¹² while the width of those excreted during exercise or while the subject was lying at an angle of 67 degrees was similar to that of casts from subjects in the early stage of glomerulonephritis.¹³ Dilatation of the renal tubules by diuresis cannot explain the observed variations in width, for in general the broader casts were accompanied with oliguria. Addis and Oliver¹⁴ have shown that a slow rate of tubular flow is one of the conditions favoring the formation of broad casts.

When the subject was standing, not only were the casts remarkably broad, but almost all were coarsely granular and fragile, during exercise or when the subject was lying at an angle of 67 degrees they were narrow and for the most part hyaline, with embedded droplets of fat or granules. Waxy and cellular casts were rarely seen. These variations suggest that the pathogenic mechanism may be different under the aforementioned conditions. Broad granular casts in the urine of a patient not in uremia should suggest the diagnosis of an orthostatic renal lesion.

COMMENT

Such inadequate tests of renal function as the concentration of urea in the blood and the excretion of phenolsulfonphthalein² are of no value in the study of orthostatic albuminuria. All of our subjects had a normal urea content of the blood, and L. S., with a creatinine clearance near the lower limit of normal and an Addis urea ratio only from 59 to 63 per cent of normal (61 per cent on another occasion) while recumbent, showed a perfectly normal identical excretion of phenolsulfonphthalein by the fractional method¹⁵ in both the supine and the erect position.

The orthostatic albuminuria in L. S. was unusually severe, in the absence of other findings, there is no reason for failing to conclude that

12 Addis, T. Renal Failure Casts, *J. A. M. A.* **84** 1013 (April 4) 1925.

13 Barnett, G. D., and Barnett, C. W. Unpublished observations.

14 Addis, T., and Oliver, J. The Renal Lesion in Bright's Disease, New York, Paul B. Hoeber, Inc., 1931, p. 140.

15 Chapman, E. M., and Halsted, J. A. The Fractional Phenolsulphonphthalein Test in Bright's Disease, *Am. J. M. Sc.* **186** 223 (July) 1933.

the diminution of the renal function was due to the orthostatic renal lesion. On the other hand, the reduction in function is not sufficient to place the diagnosis in doubt without other evidence, the final criterion is the *complete* quantitative normality of the urinary sediment while the subject is recumbent. Similarly, O B, with a hypoplastic left kidney, showed an Addis urea ratio that was only 77 per cent of normal. Conversely, J P showed large renal shadows roentgenologically, high rates of glomerular filtration and an Addis urea ratio 122 per cent of normal.

The reduction of the Addis urea ratio and the glomerular filtration rate for L S and K B when they stood was in accord with the excretion of diodrast, while neither the function test nor the diodrast test showed any significant changes in O B and J P when they stood. The relatively small reduction of function in J C was not correlated with significant changes in the excretion of diodrast. It should be noted that neither O B nor J P showed any measurable proteinuria during the part of the function test when they were erect.

The pulse pressure of our subjects varied from 10 to 27 mm of mercury when they were in the erect position, but there was no correlation between the diminution of the pulse pressure and the intensity of the orthostatic renal lesion. Without the use of diodrast, all of our subjects would have shown evidence compatible with the circulatory hypothesis. While a low pulse pressure and hemoconcentration may, theoretically at least, play an incidental rôle in the pathogenesis of orthostatic albuminuria, the demonstration by means of diodrast of unilateral changes following a change in posture in two cases and of gross renal anomalies in two others affords strong confirmatory evidence for the mechanical theory.

The finding of a reduced function by adequate tests and the association with unexpected gross renal anatomic anomalies again bring up the question of the prognosis in cases of orthostatic albuminuria. The prognosis is obviously altered by the nature of the anomalies (such as a predisposition to hydronephrosis or infection) and cannot be as optimistic in all cases as current opinion would have it. Because of the variable conditions found in such a high incidence of our unselected subjects, the prognosis should be based on a roentgenographic study by means of diodrast and rigid tests of the renal function in each case.

These findings further suggest that true orthostatic albuminuria should not be classed with "benign" albuminuria which is said to disappear as the subject grows older.

CASE REPORTS

Leslie S, aged 15, had never had hematuria, albuminuria, edema, scarlet fever or severe tonsillitis. Headaches for eighteen months and an attack of syncope caused him to go to a physician one month before the present study was made.

Albuminuria was found in an afternoon specimen, and a diet was prescribed. He appeared to be perfectly healthy (172 cm tall, weighing 58.1 Kg). The pulse rate was 60, and the blood pressure was 100 systolic and 70 diastolic. The fundi and heart were normal, the radial pulse was soft, the kidneys were not palpable and no edema or varicocele was noted. The back showed slight lumbar scoliosis, with convexity to the left, but no abnormal lordosis. The blood count, stools, basal metabolic rate and sedimentation rate were normal. The Wassermann reaction was negative. Eighty per cent of the injected congo red remained in the serum after one hour. The concentration of the plasma protein was 6.3 per cent, the cholesterol content, 161 mg per hundred cubic centimeters, and the urea content (six hours after the administration of 20 Gm of urea), 45 mg per hundred cubic centimeters.

Kenneth B., aged 19, gave no history of significance. Albuminuria was discovered during a routine examination at school two years prior to the present study, and it diminished or disappeared during rest in bed. The patient was asked to enter the hospital for study, as a diagnosis of orthostatic albuminuria had been made nine months previously. He appeared to be well (170 cm tall, weighing 58 Kg). The pulse rate was 70, and the blood pressure was 115 systolic and 85 diastolic. The fundi and the heart were normal, the radial pulse was soft, the kidneys were not palpable and no edema or varicocele was noted. Lumbar lordosis was marked but not pathologic. The blood count and stools were normal. The concentration of urea was 27 mg per hundred cubic centimeters of blood. The Wassermann reaction was negative.

Odell B., aged 34, gave no past history of significance, except that the results of a urinalysis were normal four years previously and an ache in the lower part of the back was made worse by an injury nine years before. Albuminuria was discovered in the course of a routine examination six weeks before the present study was made. The subject appeared to be well (173 cm tall, weighing 74.3 Kg). The pulse rate was 76, and the blood pressure was 125 systolic and 80 diastolic. The fundi and heart were normal, the radial pulse was soft, the right kidney was barely palpable and no edema or varicocele was noted. The lumbar portion of the spine lacked normal lordosis. The Wassermann reaction was negative. The concentration of urea was 28.8 mg per hundred cubic centimeters of blood.

John P., aged 18, gave no past history of significance, except for the normal results of urinalysis four years before the present study was made. Albuminuria was discovered during a routine examination two years before his admission to the hospital. It decreased during rest in bed but increased when normal activity was resumed. Rest in bed was again prescribed and resulted in a diminution of the proteinuria. The subject appeared to be well (183 cm tall, weighing 74 Kg). The pulse rate was 75 and the blood pressure 130 systolic and 75 diastolic. The fundi and heart were normal, the radial pulse was soft, the kidneys were not palpable even when the patient was erect and no edema or varicocele was noted. No exaggeration of lumbar lordosis was present. The concentration of urea was 36.1 mg per hundred cubic centimeters of blood.

John C., aged 20, gave no significant past history. Albuminuria was discovered one month before his entry, following a febrile illness due to involvement of the respiratory tract. A special diet and restriction of activity were prescribed. He appeared to be well (175 cm tall, weighing 61.8 Kg). The pulse rate was 88, and the blood pressure was 150 systolic and 80 diastolic. The fundi and heart were normal, the radial pulse was soft, the kidneys were not palpable and no edema or varicocele was noted. There was no exaggeration of lumbar lordosis.

but there was slight scoliosis to the left. The basal metabolic rate was normal, and the concentration of urea was 25.3 mg per hundred cubic centimeters of blood.

SUMMARY AND CONCLUSIONS

The same five subjects with orthostatic albuminuria who had been studied roentgenographically after the injection of diodrast were studied with regard to the Addis urea ratio, the Rehberg glomerular filtration rate and the Addis count of the urinary sediment.

In the two subjects in whom unilateral changes related to posture were revealed roentgenographically, the Addis urea ratio and the glomerular filtration rate fell in the second hour with the subject erect to approximately one-half the original level with the subject recumbent. In one of these subjects, who had unusually severe albuminuria, the results of the function test were diminished even when he was supine. In the two subjects with gross anomalies, posture did not affect the renal function. In the fifth case there was a 20 per cent fall in the renal function when the subject stood.

In these cases, in addition to proteinuria, standing erect results in the appearance of large numbers of renal epithelial cells and broad granular and hyaline casts in the urinary sediment, a small increase in the red blood cell count occurs inconstantly and congo red escapes into the urine. In brief, there is a transitory renal degenerative lesion.

ABSORPTION OF FAT FROM THE ILEUM IN HUMAN BEINGS

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AND

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There have been a large number of reports on the absorption of fat from an isolated intestinal loop in animals, but apparently there is no record of similar observations for human beings. Recently, an opportunity to make such studies was presented by a patient who had accidentally acquired a temporary Thury fistula of the middle portion of the ileum during treatment for strangulated femoral hernia.

REPORT OF A CASE

History—A man aged 50 was admitted to the hospital with a strangulated femoral hernia on the left side. At operation, owing to the patient's poor condition and to the fact that the strangulated loop of bowel was gangrenous, resection was not carried out, *Vorlageung* being performed instead. A tube was inserted into the proximal loop, and a fistula was allowed to form. After four weeks reoperation was performed. Through an abdominal incision both the proximal and the distal loop involving the fistula were divided, and the ends were closed. A side to side anastomosis was then made to restore the continuity of the intestine (fig 1). At this point the patient's condition became very poor, so the two limbs of the resected loop were left intact, to be removed later. The result was that an afferent and an efferent loop, each about 8 inches (20 cm) long and opening just below the left inguinal ligament, were left intact, together with the blood and lymph supply.

Experimental Procedure—Observations were subsequently carried out to determine the rate of absorption of fats from the ileum, both in the absence and in the presence of various pure bile acids.

Oleic acid and olive oil were injected into the efferent loop, and the amount of resorption was estimated for various periods. In some of the observations pure bile acids also were added. In order to produce an efficient closure of the intestinal loop, a special apparatus was constructed (fig 2). About 6 inches (15 cm) of a number 12 catheter was passed through a flat rubber pad, 2 by 2 inches (5 by 5 cm) square. One inch (2.5 cm) below the rubber pad, a balloon of condom rubber was constructed to encircle the catheter. A piece of fine catheter (number 24) was attached to the balloon for purposes of inflating it. This also passed through the rubber pad. To close off the intestinal loop, the catheter was inserted up to the rubber pad. The balloon was then inflated, and its distention tended to push it farther into the loop. The result was that the rubber pad was

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forced firmly against the opening, which was constricted, owing to its passage underreath the inguinal ligament. The efferent loop was used, since the direction of the peristaltic action tended to keep the tube in place.

Observations were always carried out in the same manner and at the same time of day. The material was injected at 10 30 a m and removed either at 1 30 p m or at 4 30 p m. As a result, only a limited number of observations could be carried out before the patient underwent the final stage of the operation—the removal of the isolated intestinal loop. At operation and on histologic section the bowel was observed to be normal, being neither distended nor inflamed.

Two hundred and fifty milligrams of gelatin was dissolved in 10 cc of water. To this was added 1 or 3 Gm of oleic acid or olive oil, and the emulsion was made up to 20 cc. To make up a solution containing bile acids, various amounts of pure cholic or deoxycholic acid were dissolved in 5 cc of water, an equivalent amount of normal sodium hydroxide being used. This solution was then mixed

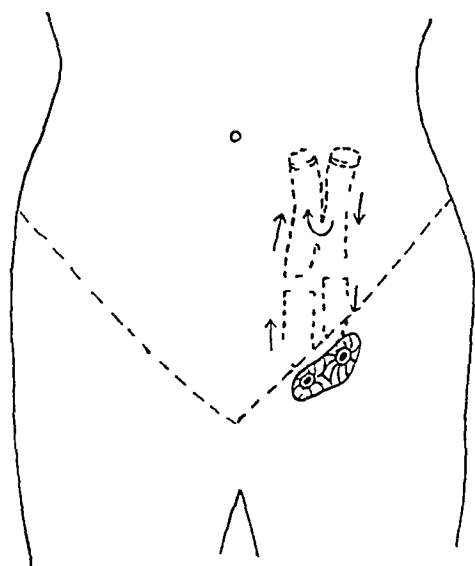


Fig 1—Diagram illustrating how two isolated loops of ileum were present after the second operation on the patient. The efferent loop was used for experimental purposes.

with the gelatin solution, the fat was added and the emulsion was made up to 20 cc. This material was then injected into the isolated loop and the tube clamped. At the end of three or six hours the contents of the loop were aspirated with a syringe, and the volume of fluid withdrawn was measured. In order to obtain any material adherent to the mucosa, the loop was washed with 20 cc of saline solution. The fat content of the saline washings was added to the total fat content. The total lipid content was estimated in each instance. Either a measured part or the total amount of the recovered fluid was precipitated with 100 cc of Bloor's alcohol-ether mixture, and the filtrate was dried to constant weight on the steam bath.

Results—Secretion of Intestinal Loop. A catheter was placed in the efferent loop, and the intestinal secretion was allowed to drain for three hours. Ten cubic centimeters of milky white fluid was obtained. On analysis this was found to contain 94 mg of lipid (9.4 mg per cubic centimeter).

Intestinal Secretion Under Experimental Conditions The tube previously described (fig 2) was introduced into the efferent intestinal loop, and the balloon was blown up, thereby sealing the opening. Twenty cubic centimeters of saline solution containing 250 mg of gelatin in solution was injected, and the tube was closed. At the end of six hours the contents of the loop were aspirated, and the loop was washed with 20 cc of water. Two experiments were carried out. In the first test 20 cc of fluid containing 405 mg of lipid was recovered, and in the second 22 cc containing 462 mg was obtained. In each case the fat content of the washings was included in the total fat content. At the end of six hours the intestinal fluid contained 21 and 20 mg, respectively, of lipid per cubic centimeter (experiments 2a and 2b).

Immediate Recovery of Fat Injected into the Intestinal Loop After the loop had been carefully washed out with saline solution, four experiments were carried out. Twenty cubic centimeters of solution containing 250 mg of gelatin and 3 Gm

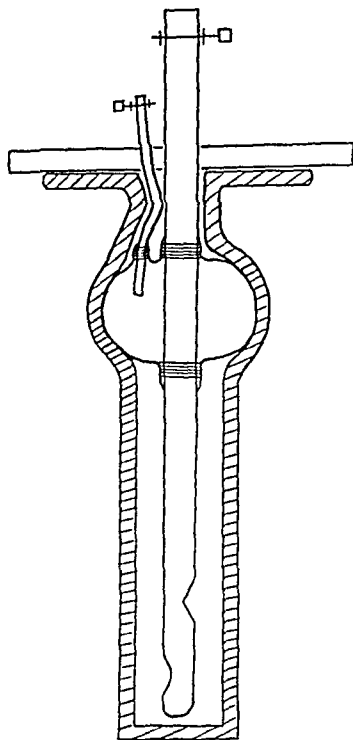


Fig 2—Diagram of the apparatus used for injecting fluid into the isolated intestinal loop. Note that the balloon on being inflated tends to pull away from the surface, since the fistulous opening is very narrow. As a result, the flat rubber pad is pressed firmly against the opening.

of either olive oil or oleic acid in the form of an emulsion was injected into the loop and then immediately withdrawn. In each case the loop was washed out with 20 cc of saline solution. The fat content of the washings was added to that of the main volume of the fluid withdrawn. As can be seen in the accompanying table (experiments 3a, 3b, 3c and 3d), injected material was recovered practically quantitatively (95.7 to 104 per cent).

Recovery of Fat After Three or Six Hours Either 1 or 3 Gm of oleic acid or olive oil emulsified with gelatin to a volume of 20 cc was allowed to remain in the loop for a period of three or six hours. As can be seen from the accompanying table (experiment 4), the volume of fluid recovered tended to be small. The percentage of loss was approximately the same whether the contents were

withdrawn at the end of three or of six hours or whether 1 or 3 Gm of fat was injected The average apparent recovery was 30 per cent

Recovery of Fat After Injection of Bile Acid Alone After the injection of bile acid alone (experiment 5) there was a large excretion of fluid over a period

Results of Various Experiments

Experi- ment	Substance Injected	Amount, Mg	Time Before With drawal, Hours	Volume of Fluid Recovered, Cc	Lipid Recovered, Mg	Percentage of Lipid Recovered
1	Intestinal secretion		3	10	94	
2a	Gelatin	250	6	22	462	
2b	Gelatin	250	6	20	405	
3a	Oleic acid	3,000	0	20	2,871	95.7
3b	Oleic acid	3,000	0	20	3,031	100.4
3c	Olive oil	3,000	0	20	3,149	104.0
3d	Olive oil	3,000	0	20	2,938	97.9
4a	Oleic acid	1,000	3	5	316	31.6
4b	Oleic acid	1,000	3	12	378	37.8
4c	Olive oil	1,000	3	5	352	35.2
Average						34.9
4d	Olive oil	1,000	6	2	288	28.8
4e	Olive oil	1,000	6	2	155	15.5
Average						22.4
4f	Oleic acid	3,000	0	15	1,796	60.0
4g	Oleic acid	3,000	6	10	759	26.3
4h	Olive oil	3,000	6	2	236	10.0
4i	Olive oil	3,000	6	2	867	28.9
4j	Olive oil	3,000	6	9	680	22.7
Average						29.6
5a	Deoxycholic acid	300	6	100	1,411	
5b	Cholic acid	300	6	15	401	
5c	Cholic acid	300	6	60	1,364	
6a	Oleic acid	3,000	3	17	1,350	45.0
	Cholic acid	50				
6b	Oleic acid	3,000	3	15	521	17.4
	Cholic acid	50				
Average				16		31.2
6c	Oleic acid	3,000	3	10	577	19.2
	Glycocholic acid	50				
6d	Oleic acid	3,000	3	10	724	24.2
	Glycocholic acid	50				
6e	Olive oil	3,000	3	26	636	21.2
	Glycocholic acid	50				
Average				15		21.2
6f	Oleic acid	3,000	3	26	720	24.0
	Deoxycholic acid	50				
6g	Oleic acid	3,000	3	34	2,382	86.1
	Deoxycholic acid	50				
6h	Olive oil	3,000	3	40	1,514	51.5
	Deoxycholic acid	50				
6i	Olive oil	3,000	3	20	863	28.8
	Deoxycholic acid	50				
Average				30		47.4
6j	Oleic acid	1,000	3	27	563	56.3
	Deoxycholic acid	300				
6k	Oleic acid	3,000	6	95	1,907	63.6
	Cholic acid	300				
6l	Olive oil	3,000	6	140	3,842	124.7
	Deoxycholic acid	300				
6m	Oleic acid	3,000	6	70	3,583	119.4
	Deoxycholic acid	300				

of six hours In the presence of deoxycholic acid there was a much greater excretion of intestinal juice than in the presence of cholic acid The second experiment with cholic acid was performed the day after the first experiment As can be seen the yield was four times as great both in volume of fluid and in total amount of fats

Injection of Fat and Bile Acids Experiments 6a to 6m show the results of the injection of fat and bile acid. The injection of deoxycholic acid with fats resulted in the largest secretion of fluid and in the recovery of the largest amount of fat. In fact, when 3 Gm of fat together with 300 mg of deoxycholic acid was injected and left for a period of three hours, more fat was recovered than was originally injected. When 50 mg of cholic or glycocholic acid was injected with 3 Gm of fat and left for three hours, the percentage of recovery was 31.2 and 21.2, while the volume recovered was 16 and 15 cc, respectively. When 50 mg of deoxycholic acid was injected with 3 Gm of fat and left for three hours, 47.4 per cent was recovered, while the volume of fluid averaged 30 cc. When 300 mg of cholic acid was injected with 3 Gm of fat and left for a period of six hours, 63.6 per cent of the fat was recovered, while the volume was 95 cc. If deoxycholic acid was used instead of cholic acid in the same quantities, 122 per cent was "recovered," while the volume averaged 120 cc.

COMMENT

Although general conclusions cannot be drawn on observations limited to one case during a short space of time, they are of some interest because of their consistency and because they appear to be the first ones made directly on the intestine of a human being.

It is well known that the small intestine secretes a fluid containing a considerable amount of fat.¹ In this case the secretion from the non-obstructed intestine contained 0.94 per cent of lipids. This figure includes the fat content of the large number of lymphocytes normally present in the intestinal secretion. Under the experimental conditions obtaining here, with the open end of the loop closed, about 21 cc of fluid was recovered in six hours. This fluid contained 433 mg, or about 2 per cent of fat. It is impossible to say whether this fat was a transudate from the blood or an actual secretion. Since the type of fat in the stool is similar to that found in the blood and in fat depots,² the inference is that it was a transudate. In that case the amount and rate of excretion of fat into the intestinal lumen should depend on the relative percentage of fat in the circulating blood as compared with the concentration of fat in the intestine. However, since the process by which fat passes through the intestinal mucosa is unknown, it is impossible to state whether the concentration of fat either in the blood or in the intestinal lumen has any influence on the secretion or absorption of fat.

The experiments indicate that olive oil and oleic acid are readily absorbed from the middle portion of the ileum in human beings in the absence of bile acids. Whether the amount of fat recovered at the end of three or six hours is an unabsorbed portion of the injected material or is the result of intestinal secretion has not been determined in these

1 Sperry, W. M., and Angevine, B. W. Lipid Excretion. IX. The Secretion of Lipids into the Intestine, *J. Biol. Chem.* **96** 769, 1932.

2 Eckstein, H. C. Fatty Acids in Subcutaneous Fat of Man, *J. Biol. Chem.* **64** 797, 1925.

experiments In considering experiments 4a to 4j, with the exception of experiment 4f, most of the figures for the amount recovered are not far off from the amount of fat excreted into the intestine under the experimental conditions In other words, the total amount of fat injected may have been completely absorbed, while the amount recovered may have been due to intestinal secretion

The effect of bile acids is very difficult to interpret The large amount of intestinal juice excreted when bile acids alone were injected (experiments 5a to 5c) may have been due either to irritation of the mucosal cells or to a physical effect of the bile acids on the mucosa Bile acids are apparently adsorbed on the surface of the mucosal cells³ However, the fat content of the fluid (21 per cent, average) was essentially similar to that of the secretion in the absence of bile acids The action of the bile acids in these experiments was to increase the volume but not the fat content of the intestinal secretion This increase in volume therefore appears to be due to irritation This may explain the varying results in the two experiments with cholic acid (5b and 5c) These experiments were performed on successive days, and the irritation produced by the first experiment (5b) may have amplified the irritative effect of the second experiment, thereby increasing fourfold both the volume and the fat content of the intestinal fluid Experiments 6f and 6g gave a similar result These were performed on successive days, and the recovery of fat in 6g was almost four times as great as in 6a Similar findings have been reported by Croner⁴ and Gumilewski⁵

When fat was injected together with small amounts of bile acids, the recovery of fat in general did not differ markedly from the amount recovered after the injection of fat alone The volume of the recovered fluid was on the average almost three times as great When large amounts of bile acids were injected together with fat, the volume of intestinal secretion was tremendously increased, in one case up to 140 cc The effect of a large amount of deoxycholic acid is well illustrated in experiments 6l and 6m, in which more fat was recovered than was injected The injection of 300 mg of deoxycholic acid alone (5a) resulted in an excretion of 1.4 Gm of fat in six hours In experiments 6l and 6m 3 Gm of fat was injected, together with 300 mg of deoxycholic acid By adding the excretion of fat produced by the action of the deoxycholic alone, there was a total of 4.4 Gm of fat actually present in the intestinal loop In these experiments the recovery of fat averaged

3 Verzar, F, and von Kuthy, A Die Bedeutung der gepaarten Gallensauren für die Fettresorption IV, *Biochem Ztschr* **230** 451, 1931

4 Croner, W Versuche über Resorption von Fetten im Dunndarm, *Biochem Ztschr* **23** 97, 1909

5 Gumilewski Ueber Resorption im Dunndarm, *Arch f d ges Physiol* **39** 556, 1886

37 Gm Therefore, 07 Gm of fat was actually absorbed during a period of six hours By stimulating the excretion of fat the result of the presence of a large amount of deoxycholic acid in the ileum in this case was to prevent the absorption of fat

The difficulty of interpreting such results is well illustrated by a short review of some of the literature Bloor, Sperry and their co-workers⁶ have shown that in animals the stool lipids are excreted in consistent amounts and are of uniform type, regardless of the diet Krakower⁷ demonstrated that the same holds true in human beings Moreover, according to Eckstein,² the fecal lipids are apparently similar in composition to those in the fat depots in each species Accordingly, it appears that fecal lipids represent an excretion of the blood into the small intestine¹ It therefore follows that all experiments of the type in which the intake is compared either with the fecal output or with the output of an isolated intestinal loop yield results which may be falsely interpreted The amount of absorption of a measured intake cannot be estimated by analyzing the stool, since the lipids in the stool are completely independent of the intake If bile is completely diverted from the intestinal tract, absorption of dietary fat is greatly decreased, but at the same time the endogenous excretion of fat is greatly increased, since even with a fat-free diet the stools in cases of complete biliary obstruction are fatty and bulky

The same factors must be considered in interpreting experiments that utilize an isolated intestinal loop The amount of fat recovered at the end of a period of time represents not only the material that has not been absorbed but also the lipid that has been excreted during that period

This confusion in interpretation is well exemplified in early experiments on isolated loops of small intestine in animals Von Furth and Schutz⁸ found that sodium oleate and stearate were poorly absorbed by cats in experiments covering periods of seven or eight hours The results were variable, although olive oil apparently could be absorbed to an extent of over 50 per cent The addition of bile apparently had little effect Croner⁴ showed that neutral fats are best absorbed in the

6 Hill, E, and Bloor, W R Fat Excretion, *J Biol Chem* **53** 171 (July) 1922 Holmes, A D, and Kerr, R H Ether Extract of Feces, *ibid* **58** 377 (Dec) 1923 Sperry, W M, and Bloor, W R Fat Excretion Quantitative Relations of Fecal Lipids, *ibid* **60** 261 (June) 1924 Sperry, W M Lipid Excretion, Further Studies of Quantitative Relations of Fecal Lipids, *ibid* **68**, 357 (May) 1926

7 Krakower, A Fecal Fat and Its Relation to Fat in the Diet, *Am J Physiol* **107** 49 (Jan) 1934

8 von Furth, O, and Schutz, J Ein Beitrag zur Methodik der Versuche über Fettresorption aus isolierten Darmschlingen, *Beitr z chem Physiol u Path* **10** 462, 1907

lower end of the small intestine He stated the opinion that the various portions of the small intestine vary both qualitatively and quantitatively in their ability to absorb fats Apparently in the lower end of the small intestine in animals fats are absorbed to an extent of 50 per cent

Plant,⁹ Veizar and von Kúthy² and Riegel and his co-workers¹⁰ have shown that the addition of bile salts greatly increases the resorption of fats from the small intestine in animals

However, in interpreting all these results three factors must be considered (1) the situation of the isolated loop, since the lower end of the small intestine seems to absorb fats much more readily than the upper end, (2) the duration of the experiment, since the residual fat is the sum of the unresorbed portion plus the amount excreted during the period of the experiment, and (3) the frequency of the experiments—both Croner⁴ and Gumilewski⁵ showed that if the loop is left alone for several days the resorption of fat is decreased in the next experiment

CONCLUSIONS

Observations on the absorption of fat from the middle of the ileum in one human subject showed the following facts

In a human being the ileum secretes a fluid which contains about 2 per cent of lipids

The presence of bile acids increases the volume of the secretion, while its lipid concentration remains unchanged

Olive oil and oleic acid are absorbed from the ileum even in the absence of bile acids

Bile acids in small amounts have apparently no effect on the rate of absorption of fats from the ileum

Deoxycholic acid in large amounts increases the volume of the excretion and so tends to reduce the rate of absorption of fat

9 Plant, O H Experiments on the Absorption of Fat from an Isolated Loop of Small Intestine in Healthy Dogs, *Am J Physiol* **23** 65, 1908

10 Riegel, C, Elsom, K, and Ravdin, I S The Influence of Sodium Taurocholate, Hepatic Bile and Gall-Bladder Bile upon the Absorption of Oleic Acid from the Small Intestine, *Am J Physiol* **112** 669 (Aug) 1935

SIMMONDS DISEASE (ANTERIOR HYPOPHYSIAL INSUFFICIENCY)

REPORT OF TWO CASES WITH AUTOPSY

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Because of the current interest in diseases of the endocrine glands and because of the comparative sparsity of reports of cases of Simmonds' disease with autopsy, the following cases are placed on record. There is included also a comparison of some of the effects of the glandular deficiency of Simmonds' disease and of the glandular hyperfunction of acromegaly.

REPORT OF CASES

CASE 1—A 51 year old housewife was admitted to the Cleveland City Hospital on April 10, 1935, in coma.

Clinical History—The clinical history was obtained from the records of the University Hospital Dispensary, where the patient was first seen on June 8, 1933. She complained then only of pain and stiffness of the knees, which were worse after disuse and improved with exercise. These symptoms began three years previously, after six months of convalescence from a difficult delivery. The menses, which had been normal, had stopped, and the patient had lost 20 pounds (9 Kg). She had been married for eight years and had one other child, aged 7 years, who was delivered by cesarean section. Physical examination revealed a small healthy-looking woman weighing 109 pounds (49 Kg). The temperature was 37.4 C (99 F). The teeth were lacking, the eyebrows, eyelashes and hair of the head were thin and no axillary or pubic hair was noted. The clinical diagnosis was arthritis, alopecia and malnutrition.

One cubic centimeter of a preparation of the anterior lobe of the hypophysis¹ weekly and hydrotherapy were advised. The patient reported irregularly and received only 20 cc of the hypophysial preparation in nine months. Fine pubic and axillary hair appeared, she gained 3 pounds (1.5 Kg) and the condition of the knees improved. On March 1934 the temperature of 36 C (96.8 F) aroused further investigation. The patient admitted chilliness and anorexia. The pulse rate was 78, and the blood pressure was 130 systolic and 80 diastolic. Pelvic examination revealed excessive postmenopausal atrophy for the patient's age. The basal metabolic rate was -33. An electrocardiogram showed an inverted T wave in leads II and III. The dextrose tolerance test showed a sugar content of 68 mg per hundred cubic centimeters of blood during fasting, one-half hour after the

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1 The preparation used was antuitrin.

ingestion of 100 Gm of dextrose the value was 116 mg, in one hour it was 120 mg, and in two hours, 105 mg. Gastric analysis showed free hydrochloric acid after the administration of alcohol and histamine. The erythrocyte count was 2,700,000, and the hemoglobin content, 63 per cent.

The hypophysial preparation was then replaced by 0.064 Gm of desiccated thyroid three times a day and a diet with a high caloric and high vitamin content. After three months of this treatment the basal metabolic rate was -26 and the temperature 36.6°C (97°F), but the weight had fallen to 100 pounds (45.5 Kg), and the patient had had a few dizzy spells. Thyroid therapy was then discontinued.

In November 1934 the patient's energy was recorded as good, the weight was 117 pounds (53 Kg) and the temperature was 34°C (93°F). In February 1935 she felt "pretty good except for pains in the knees." The weight was $119\frac{1}{2}$ pounds (54 Kg), and the temperature was 34°C (93°F).

Six weeks later, five days before being admitted to the City Hospital, the patient began to vomit and was unable to retain anything until the night before her admission to the hospital, when she took a little orange juice. She was in coma for several hours before being taken to the hospital.

Physical Examination—The patient was comatose, pallid and covered with perspiration. Breath was slow and shallow. The extremities were cold, and the knees were rigidly flexed but could be forcibly straightened out. No body hair was present. The heart sounds were distant. The temperature was 34.4°C (94°F), the pulse rate 84 and the respiratory rate 16. The blood pressure was 140 systolic and 80 diastolic.

Course—The patient was given 60 cc of a 50 per cent solution of dextrose intravenously. A generalized convulsion occurred three hours after the patient's admission to the hospital. Respirations stopped but began again after stimulants had been given and artificial respiration had been instituted. The patient died ten hours after her admission to the hospital.

Laboratory Findings—Analysis of the blood showed sugar, 21 mg per hundred cubic centimeters, carbon dioxide, 48.5 volumes per cent, chlorides, 104 mg, sodium chloride, 172 mg, and urea nitrogen, 6 mg. The urine showed a specific gravity of 1.023, albumin and a few leukocytes.

Clinical Diagnosis—The diagnosis was hypoglycemia of unknown cause.

Autopsy—Autopsy was performed four hours after the patient's death by one of us (M. G.). The body was well developed and moderately well nourished, measuring 170 cm in length and weighing approximately 110 pounds (50 Kg). The skin and mucous membranes were pale and without any unusual pigmentation or discoloration. There was a conspicuous absence of pubic and axillary hair, the hair on the head was fine, brown and not abundant. The eyebrows and eyelashes were thin. The breasts were small and well developed. A moderate amount of yellow subcutaneous fat was exposed on section. The heart weighed 200 Gm and showed slight coronary arteriosclerosis. The aorta had a roughened, gelatinous intimal surface and microscopically showed irregular erosion of the intima and swelling and granular degeneration of the fibrous tissue of the intima and media. The lungs showed a small focus of early bronchopneumonia. The liver weighed 850 Gm, and the small lobules were made up of compact parenchymal cells. The spleen weighed 125 Gm and had a slightly thickened capsule. Histologically a few malpighian bodies were seen to contain secondary nodules of dark brown, pigment-laden phagocytes. The kidneys weighed 75 Gm each and histologically showed slight arterionephrosclerosis in an unusually compact tissue. The bladder was the seat of slight chronic inflammation.

The hypophysis with attached meninges and dura weighed 0.55 Gm, the weight of the hypophysis alone being estimated as 0.45 Gm. Histologically (fig 1A) the anterior lobe showed extreme atrophy. The interstitial framework was vaguely present in some situations, and although the acini were almost completely replaced by a granular, filmy, light eosinophilic substance, a rare ill defined cell group could be made out. In the infundibular region was a small area of acinar cells that were better preserved. These cells contained much lipid in fine to coarse droplets, and with Mallory's stain for connective tissue 97.6 per cent were chromophobic, 0.9 per cent were basophilic and 1.5 per cent were eosinophilic cells. Some of the acini contained colloid, and in the pars intermedia were cystlike spaces filled

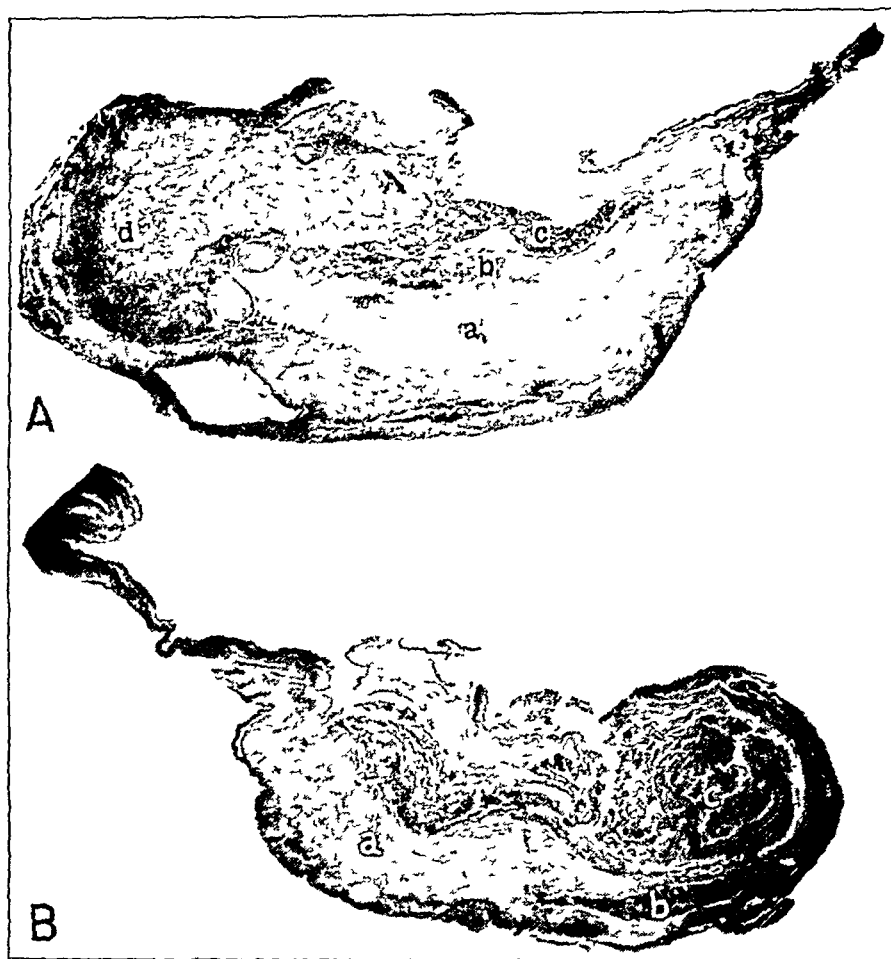


Fig 1—The pituitary gland, $\times 10$, hematoxylin and eosin stain. A, cross-sections (case 1) showing (a) an atrophic fibrotic anterior lobe with (b) a zone of hemorrhage and (c) a small remaining island of cells of the anterior lobe and (d) of the posterior lobe. B, cross-section (case 2) showing (a) an atrophic fibrotic anterior lobe with (b) a narrow band of preserved cells of the anterior lobe and (c) of the posterior lobe.

with colloid and lined with cuboidal epithelium. Between the preserved and the atrophic portion of the anterior lobe was an area of hemorrhage in the connective tissue, and brown pigment-laden phagocytes were present in the adjacent fibrous tissue. The posterior lobe showed gliosis which became marked peripherally. The nerve fibers were markedly reduced in number. The entire capsule of the

hypophysis was thickened and fibrous and contained elongated channels lined with flattened epithelium and surrounded by small areas of hemorrhage

The pineal body weighed 200 mg, it was yellowish gray, cone shaped and on section finely granular. Histologically, bands of fibrous tissue and neuroglia separated follicular groups of cells which had dark, dense to vesicular nuclei and ill defined eosinophilic cytoplasm, occasionally stippled with basophilic or brown pigment granules. Several corpora arenacea were present.

The thyroid gland weighed 135 Gm and was not grossly fibrous. Histologically (fig 2A) it showed eosinophilic, dense, colloid-filled acini which were unequal in size, generally small and lined with low cuboidal to flat epithelium containing lipoid. There was diffuse interlobular and intralobular fibrosis. There was no conspicuous lymphocytic infiltration. The intralobular capillaries were markedly reduced in number, and the interlobular vessels were surrounded by connective tissue.

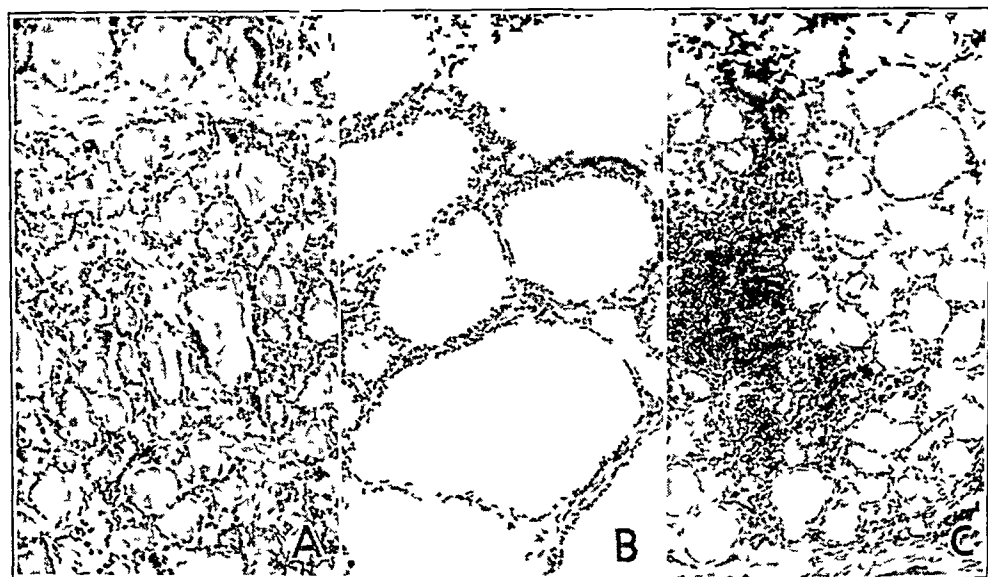


Fig 2—Photomicrographs of cross-sections of the thyroid gland, hematoxylin and eosin stain, $\times 150$. A, Simmonds' disease (case 1) B, acromegaly, C, Simmonds' disease (case 2)

Two very small parathyroid glands were present. Histologically (fig 3A) they were composed almost entirely of irregular anastomotic groups of small transitional water-clear cells.² In the cytoplasm of these cells was a lipoid-staining area which in some cells was homogeneous and in others granular. This area was about half the size of the nucleus. These groups of cells were separated by similarly disposed, slightly less extensive adipose tissue. A distinct acinar arrangement of slightly larger water-clear cells was present in one small, poorly delimited area. These cells were pyramidal and rested on a distinct basement membrane, with the apexes reaching the center of the lumen. In a rare acinus there was a small amount of colloid. Between these acini was a moderate amount of

² This is the terminology used by B. Castleman and T. B. Mallory (*Am J Path* 11 1, 1935)

connective tissue. One small compact group of pale oxyphilic cells and a few scattered oxyphilic cells were seen. Nonvacuolated principal cells were rare. Small blood sinuses were moderately numerous.

The pancreas weighed 40 Gm. The number of islets per microscopic field was relatively increased. The islets were of average or slightly reduced size and were made up of compact cells that were otherwise normal in appearance. The acinar cells were not unusual. The lobules were small and compact, with moderately prominent, but not thickened, connective tissue septums.

The adrenal glands weighed only 3 Gm. each. On section the cortex was seen to be made up of two rather distinct zones. The outer of these was a semi-translucent yellowish brown tissue, the inner, which measured from 0.5 to 1 mm in thickness, had the appearance of adrenal cortex. The medulla measured 5 mm in thickness centrally.

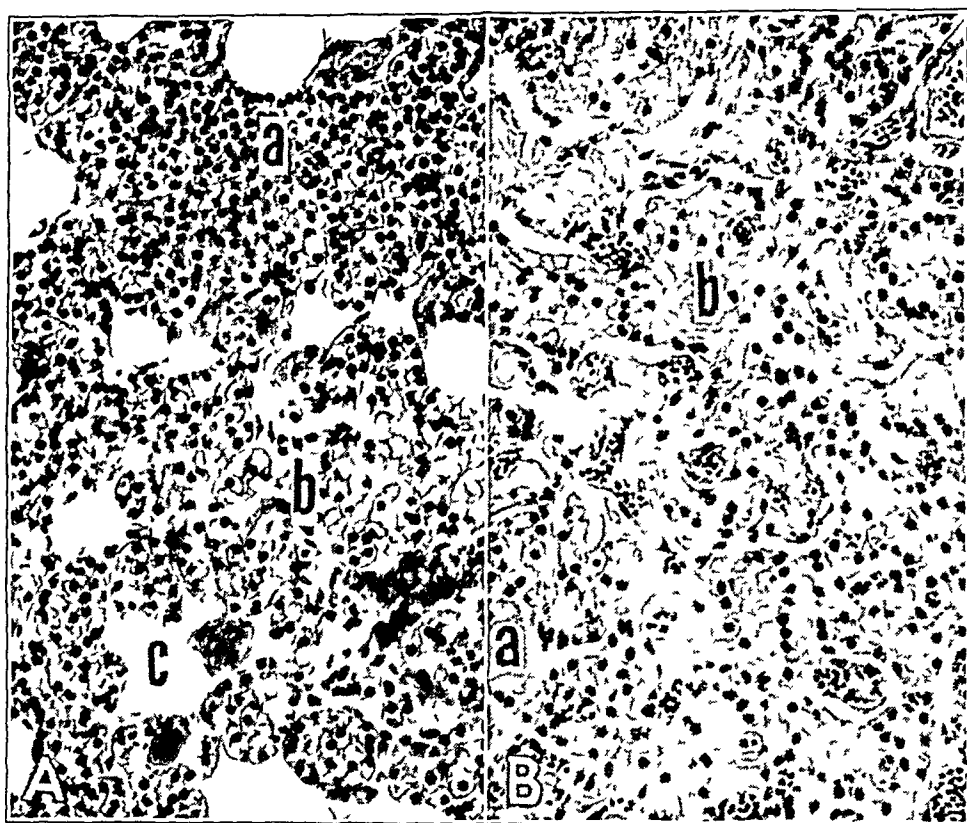


Fig. 3—Parathyroid glands, hematoxylin and eosin stain, $\times 250$. A, Simmonds' disease (case 1), showing (a) transitional water-clear cells, (b) an adenomatous area of water-clear cells and (c) adipose tissue. B, acromegaly, showing (a) a few transitional water-clear cells and (b) transitional oxyphilic cells.

Histologically (fig. 4A) the capsule was thickened with dense fibrous tissue, which occasionally enmeshed groups of glomerular zone cells and extended along the interstitial tissue to the medulla. The cortex was markedly narrowed in all zones.

The zona glomerulosa was lacking in many areas, while in others it showed the usual architecture. The small cells contained finely granular, moderately dense eosinophilic cytoplasm with fine lipid droplets. There were some round, thin nuclei and some smaller, slightly irregularly shaped, dense basophilic nuclei.

The zona fasciculata showed a reduction of the length and number of cells in the individual columns. The cells were polygonal and contained lipid-filled, faintly eosinophilic staining cytoplasm and round, finely stippled basophilic nuclei. Rarely such columns were grouped together in an adenoma-like area. There were a few narrower columns of dark eosinophilic cells with finely distributed lipid. Between these two types were intermediate stages, all types containing lipid, for the most part in large dense globules.

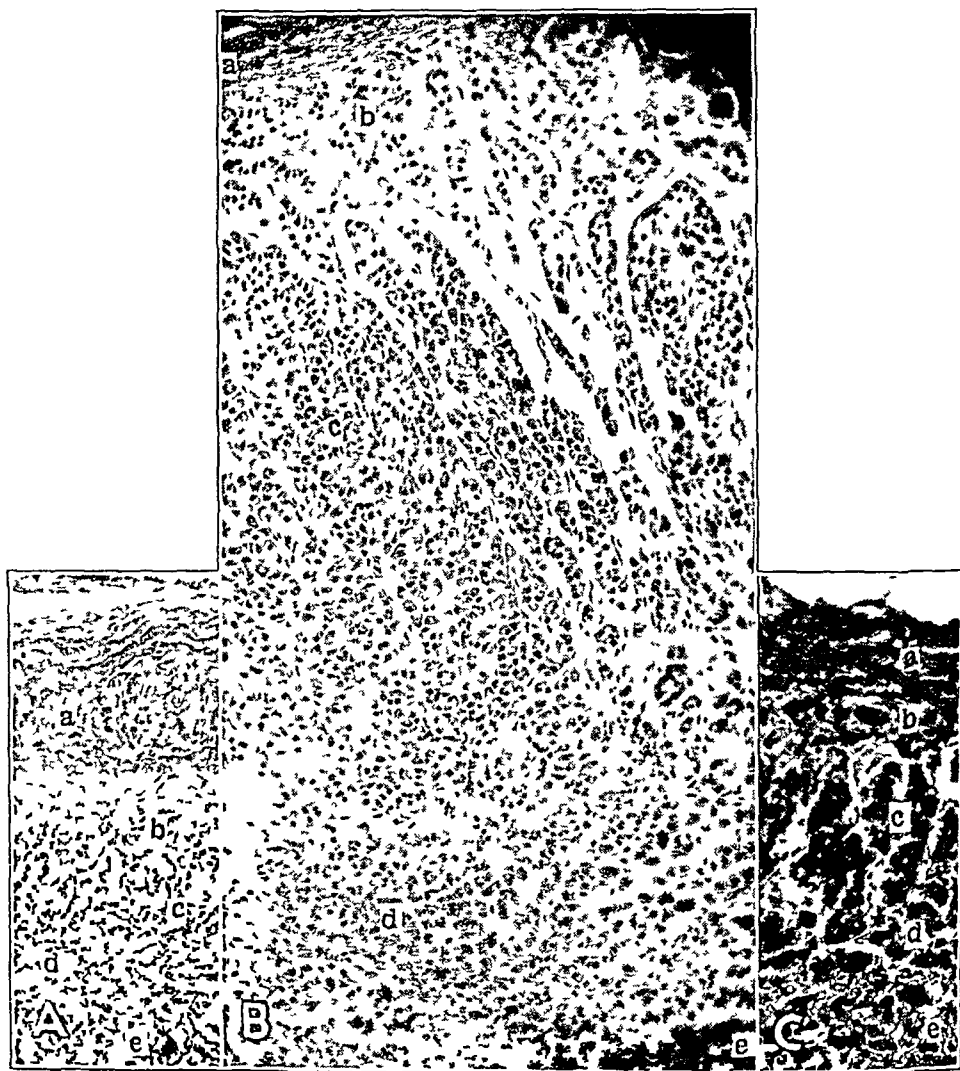


Fig 4—Adrenal glands, hematoxylin and eosin stain, $\times 150$. The appearance in Simmonds' disease, case 1 (A) and case 2 (C), compared with that in acromegaly (B). *a* indicates capsule, *b*, zona glomerulosa, *c*, zona fasciculata, *d*, zona reticularis, and, *e*, medulla.

The reticular zone showed a marked increase in fibrous tissue and encapsulated the medulla. The cortical cells scattered in this thickened reticulum had less cytoplasm but were otherwise similar to those first described in the zona fasciculata. Rarely was there a group of compact eosinophilic cells with dense, round basophilic nuclei. A few cells contained fine, light brown pigment.

The medulla showed no fibrosis or apparent atrophy. There was a moderate amount of lipid in many of the cells.

The uterus weighed 19 Gm. Histologically the endometrium consisted of a single layer of cuboidal cells, with underlying compact fibrous tissue. In the latter tissue were scattered channels lined with cuboidal epithelium. The tubes were cordlike and lined with cuboidal to columnar ciliated epithelium.

The ovaries weighed 1.5 Gm each. Microscopically they consisted of dense cellular connective tissue without follicles, of corpora albicantia and of thick-walled blood vessels. In the left ovary were a few channels lined with cuboidal epithelium similar to those seen in the uterus.

In the histologic examination of the axillary and pubic skin no apocrine glands were identified. The epithelium was thin, and the papillae were infrequent. The dermis was compact. There were occasional hair follicles and some were surrounded by compact fibrous dermis. The few sebaceous glands had vacuolated cells and were surrounded by a hyaline capsule. In the subcutaneous tissue were sudoriparous glands and ducts distended with eosinophilic fluid.

The central nervous system was minutely examined. With the Nissl stain, the pia arachnoid showed green granules lying in the cytoplasm of the mesothelial cells and in phagocytic cells lying free in the tissues.

The cerebral cortex showed a diffuse change in the ganglion cells characterized by shrinkage of the cells, with deeply stained triangular or oval nuclei and pale blue homogeneous cytoplasm without Nissl granules or lipid pigment. The Bielschowsky stain revealed argentophilia of the nuclei of these cells but no fibrillary degeneration or senile plaques. In other cells fine metachromatic granules or deep blue granules appeared to be lying in vacuolated cytoplasm. Cells with pale, swollen nuclei, displaced nucleoli and faintly stained metachromatic cytoplasm appeared in the same field with the cells just described (fig 6A and B). These changes in the ganglion cells were most pronounced in the second, third and fourth cortical layers. The agranular central cortex was the region least affected. Small circumscribed areas of cellular defects (*Verodungsheide*) and diffuse cellular defects were present in many regions (fig 5).

The fixed glia tissues contained many progressive macroglia cells with large clear nuclei and cytoplasm containing fat-staining green pigment granules. These cells showed no fibril production with the Holzer stain. In some areas of the white matter fat droplets were present in the glia cells. The molecular layer of the cortex contained regressive microglia cells and astrocytes. The capillary walls contained an excessive amount of fat, while the larger blood vessels exhibited perivenous round cell infiltration in many areas (fig 6C). Periarterial collars of fat filled gutter cells and abundant fat in the adventitia cells were seen, especially in the white matter and the projection pathways. No arteriosclerosis was present. The Nissl stain revealed in the anterior commissure peculiar deep blue homogeneous globules lying along the myelinated fibers.

In other regions besides the cortex changes similar to those described were noted in the ganglion cells but were less extensively distributed. The basal ganglions also contained many astrocytes with fat granules in their cytoplasm. The cerebellum showed only pigment granules in the leptomeninges and the accumulation of products of degeneration around the arteries in the white matter.

Significant changes were observed in the hypothalamus. Serial sections made through this region and compared with similar sections of normal brains revealed a total loss of axis-cylinders in the tuber cinereum coming from the pars nervosa.

of the hypophysis³ The nucleus supra-opticus showed a marked loss of cells, as compared with the normal condition, and those present exhibited a vacuolar type of degeneration (fig 6) The supporting tissue consisted of large fibrillary astrocytes and abundant glial fibrosis No colloid material, such as was described by Scharrer,⁴ was present in the cells or supporting tissues The tract of unmyelinated fibers supposed to connect the nucleus supra-opticus with the pars nervosa of the hypophysis could not be identified in the sections or traced in

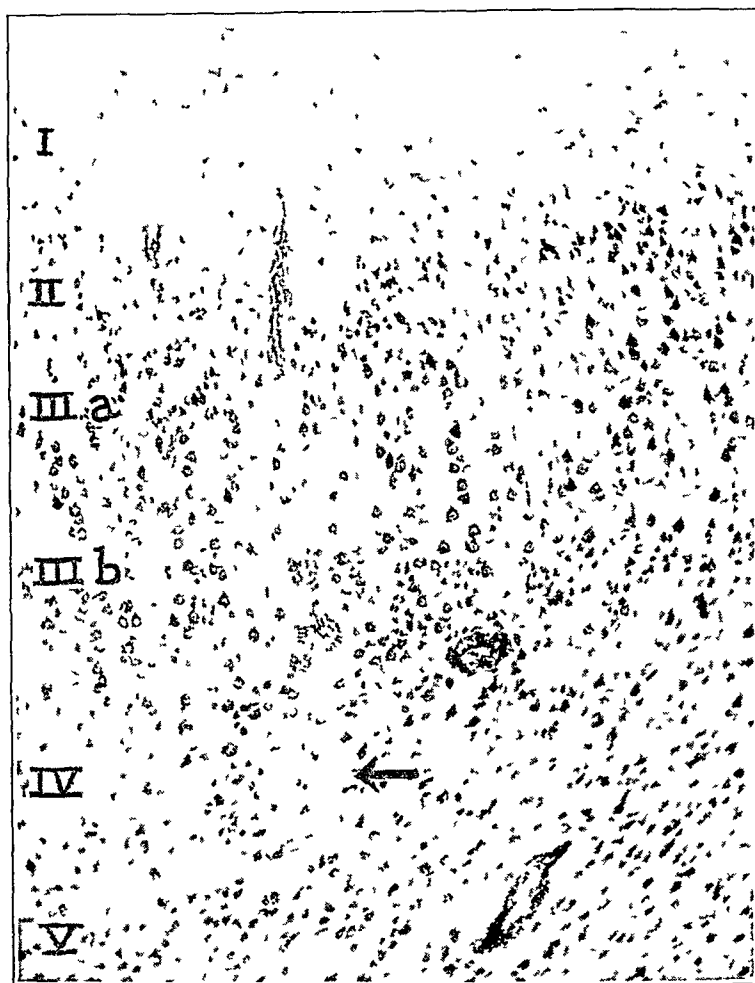


Fig 5—The posterior insular region of the cerebral cortex, Nissl stain, $\times 85$ The arrow indicates a small circumscribed cellular defect in lamina IV Below and to the right is a small vessel with round cell infiltration

normal material, but the changes seen in the nucleus supra-opticus offered presumptive evidence of such a connection The number of cells in the nucleus para-

3 Serial sections were made of frozen material in order to obtain more satisfactory Bielschowsky preparations This entailed considerable technical difficulty

4 Scharrer, E Die Erklärung der scheinbar pathologischen Zellbilder im Nucleus supraopticus und Nucleus paraventricularis, *Ztschr f d ges Neurol u Psychiat* 145 462, 1933

ventricularis was not reduced, and there was only the type of cellular changes noted in the cortex. No relationship of this nucleus to the pars nervosa of the hypophysis could be identified.

Records of 1 other case in which a diagnosis of Simmonds' disease could be made were found in reviewing the protocols of 7,000 autopsies

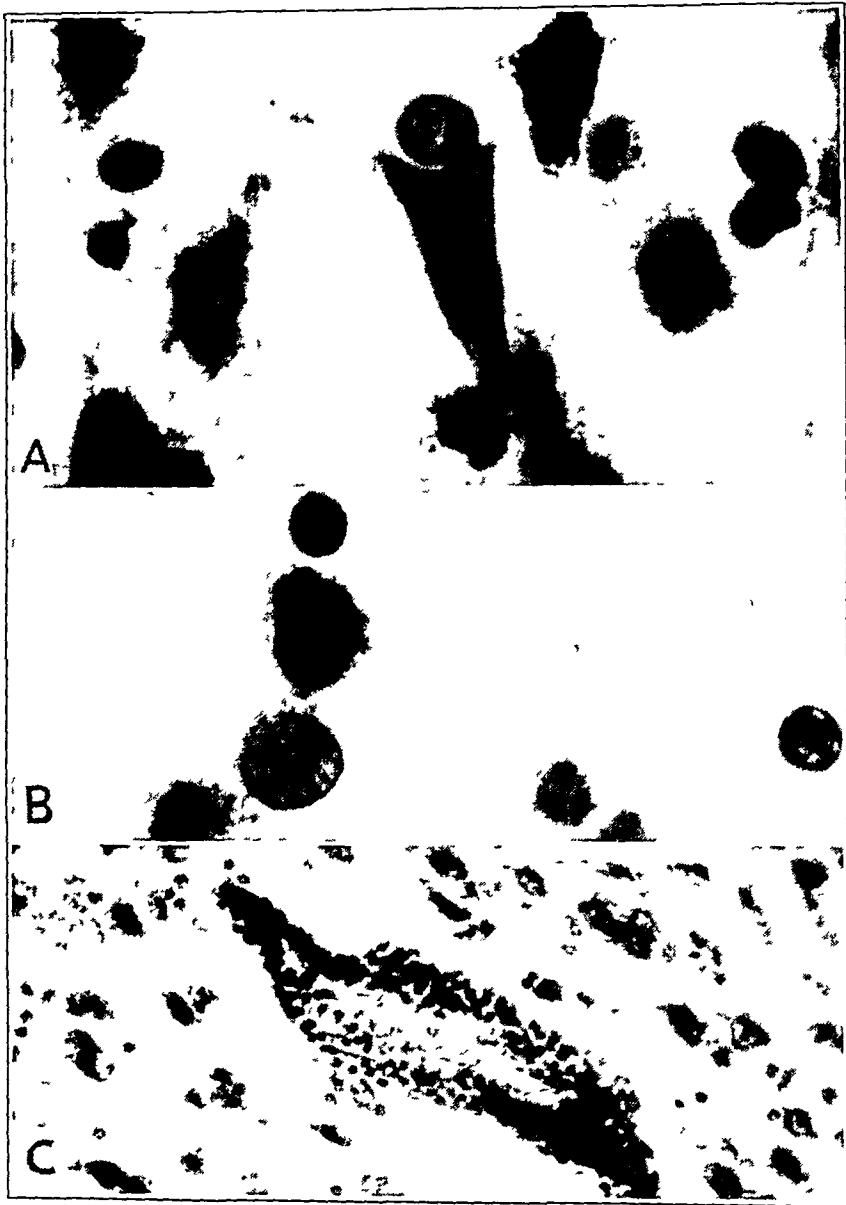


Fig 6—*A*, posterior central gyrus, $\times 2,250$. Note the severely shrunken cells with glial satellite. *B*, the parietal region, $\times 2,250$. Note the ganglion cells with a loss of Nissl granules, faintly stained cytoplasm and changes in the nuclei described in the text. *C*, an area of round cell infiltration shown in figure 5, $\times 300$.

at the Cleveland City Hospital and the files of 5,400 autopsies at the Institute of Pathology of the University Hospitals. That case is herewith reported.

CASE 2—A 60 year old white woman entered the University Hospital on Oct 5, 1934, in an irrational state The history was obtained from the daughter

Clinical History—The patient was married at the age of 19 She had had one miscarriage and six normal deliveries When she was 32 years old, toxemia of pregnancy was followed by the menopause For twelve years she had weekly "sick headaches," urinary frequency and nocturia

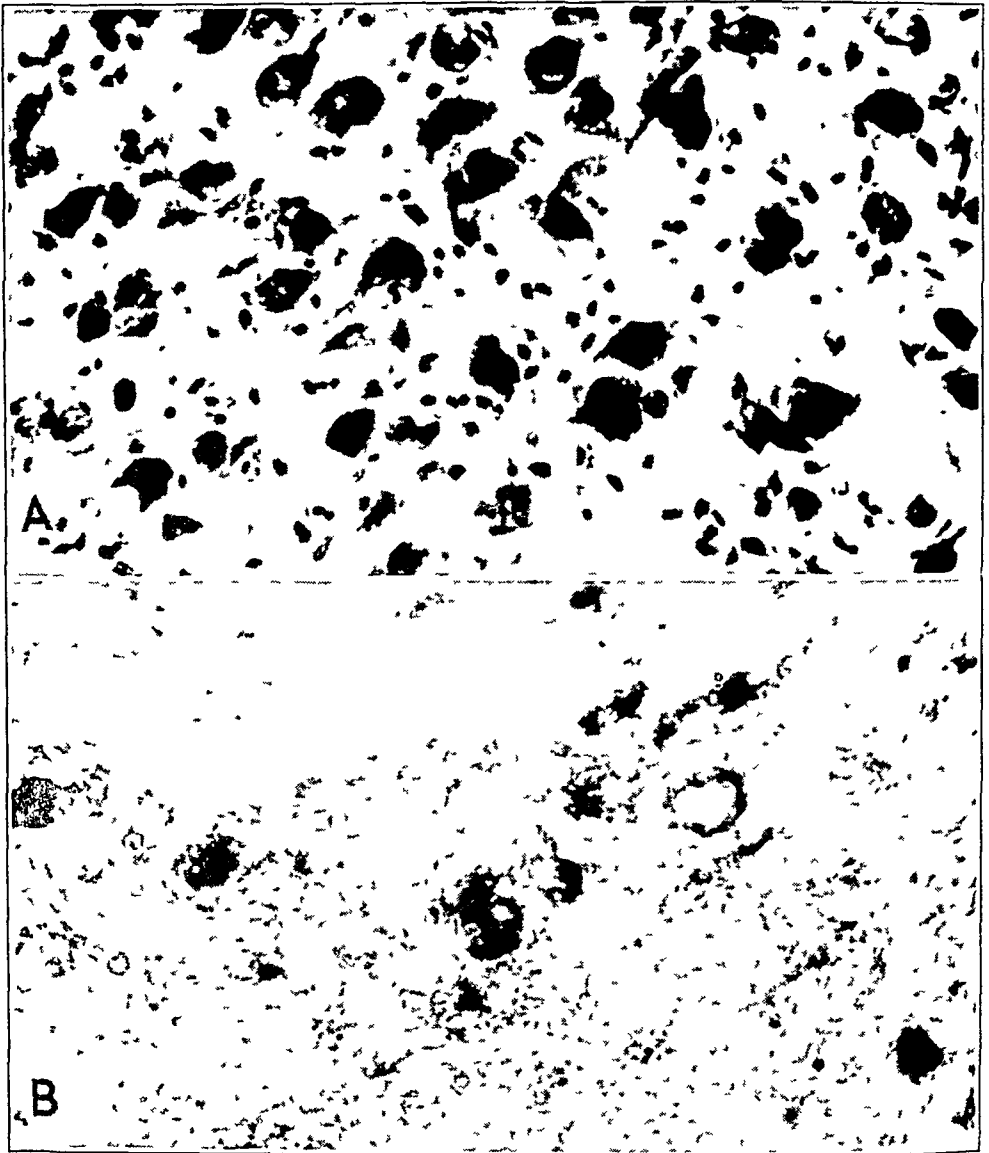


Fig 7—Nucleus supra-opticus, Nissl stain, $\times 300$ A, normal brain, B, Simmonds' disease Note the loss of ganglion cells, with vacuolation and degeneration of the cells present, and the faintly stained fibrillary astrocytes

Two years before her admission to the hospital she suddenly had chills and fever and in a few days became irrational During six weeks of hospitalization at that time these unexplained symptoms gradually subsided All the teeth were extracted because of severe caries Similar transient episodes occurred during the next five months Another attack nine months before her final admission to

the hospital lasted for three weeks and was followed by pains in the knees. These pains had led to incapacitating flexion of the knees for the last seven months.

Two and a half weeks before admission to the hospital the patient showed fatigue, slowness of speech and drowsiness, which in four days progressed to coma with retention of urine. This was followed by an irrational incontinent state without convulsions or paralyses.

Physical Examination—The patient was an elderly, well developed and fairly well nourished woman. She moaned and cried and was irrational. The skin was fine, soft, dry and pale and vaguely suggested the appearance of brawny edema. The eyebrows and the axillary and pubic hair were scanty. The teeth were absent. The heart was enlarged slightly to the left, and there was a soft systolic murmur over the precordium. The blood pressure was 90 systolic and 55 diastolic. The liver was enlarged, extending 3 fingerbreadths below the costal margin. The legs were not atrophic but were held stiffly in 90 degree flexion, with apparent voluntary contraction of the hamstring muscles. The temperature was 37.8 C (99 F). The pulse rate was 70 and the respiratory rate 18.

Laboratory Findings—The urine was loaded with leukocytes. The blood showed erythrocytes, 3,500,000, hemoglobin, 83 per cent, and leukocytes, 4,950. The Wassermann test of the blood was negative. The protein content of the plasma was 6.61 Gm, with an albumin-globulin ratio of 1.1. The blood contained 14 mg of urea nitrogen per hundred cubic centimeters. Gastric analysis showed free hydrochloric acid during fasting. A phenolsulfonphthalein test showed a 5 per cent output during the first hour and a 10 per cent output during the second hour.

Course—Treatment consisted of inserting an inlying catheter and irrigations of the bladder. The temperature for the first five days was elevated to 39.8 C (103 F), after which it fell to between 37 and 37.5 C (98.6 and 99.5 F). The slightly myxedematous appearance of the skin and infrequent shallow respirations, even with fever, suggested thyroid deficiency. The basal metabolic rates obtained on the fifth, sixth and seventh days of hospitalization were —16, —36 and —34, respectively. Twice a day 0.032 Gm of desiccated thyroid was given, the dose being increased to 0.064 Gm on the tenth day and further increased to three times daily on the sixteenth day. The basal metabolic rates on the twelfth and fourteenth days were —13 and —34, respectively. Electrocardiographic studies showed a leucardiogram. The PR interval was 0.16 second and the QRS interval 0.08 second. The rate was 82, and there was slurring in leads II and III, with a diphasic contour in lead III.

The mental state cleared for a while to the point of rationality. Later the patient became lethargic, irrational and finally comatose. These symptoms were accompanied with a drop in the blood pressure (from 144 systolic and 86 diastolic to 90 systolic and 62 diastolic) and elevation of the pulse rate (from 76 to 120) and temperature (to 40.5 C, or 105 F), terminating in death.

A study of the blood made on the day of death showed urea, 23.4 mg, sugar, 74 mg, carbon dioxide, 59.4 volumes per cent, leukocytes, 14,600, neutrophils, 57 per cent, lymphocytes, 26 per cent, eosinophils, 10 per cent, basophils, 3 per cent, and monocytes, 4 per cent.

Clinical Diagnosis—The diagnosis was pyelocystitis, myxedema and toxic psychosis.

Autopsy—Dr G. A. Tischer performed the autopsy five hours post mortem. The body was well developed and moderately well nourished. It weighed 50.5 Kg and measured 157 cm in length. The skin was of normal consistency and did not feel thickened. The breasts were small, the genitalia were those of an adult.

woman The hair was scanty The heart weighed 290 Gm and showed chronic rheumatic disease with mitral stenosis The aorta showed intimal plaques with calcification There was pulmonary emphysema The liver weighed 1,400 Gm and microscopically showed subacute periportal hepatitis and an advanced degree of arteriolar sclerosis A gallstone in the ampulla of the gallbladder completely obstructed the cystic duct The urinary system was the seat of chronic and acute pyelonephritis and cystitis The kidneys weighed 130 Gm each The gastrointestinal tract showed no significant abnormality

The hypophysis was very small and difficult to recognize Histologically (fig 1 *B*) the capsule of the posterior lobe was markedly thickened with fibrous tissue, it was sharply demarcated from the pars nervosa, which was proportionately decreased in size The anterior lobe was almost completely replaced by thin, loose, moderately acellular connective tissue in which, adjacent to the pars intermedia and extending peripherally along one side, was a bandlike area containing groups of acinar cells These cells were not sharply delimited and contained much lipid, chiefly in large globules Mallory's stain for connective tissue showed 98.1 per cent chromophobes, 1.6 per cent eosinophils and 0.3 per cent basophils A few acini filled with colloid and lined with low cuboidal epithelium were present in the intermediate zone

The pineal body measured 9 by 15 mm The tissue was made up of follicular groups of interneuroglia and neuroglia cells, the latter being more abundant The stroma in some areas was reticulum-like and contained only a few scattered neuroglia cells Several corpora arenacea were noted

The thyroid weighed 17 Gm and appeared to be poor in colloid Histologically the follicles varied little in size They contained a moderate amount of colloid and were lined with flattened epithelium There was intralobular and perilobular fibrosis, with marked lymphocytic infiltration and several large lymph follicles There was moderate arterial and arteriolar sclerosis

The parathyroid tissue included in the section of the thyroid gland showed principal cells and a few groups of oxyphilic and transitional water-clear cells One moderately large area showed cuboidal principal cells forming acini filled with dense eosinophilic colloid Adipose tissue was scattered throughout, arteriosclerosis was marked and small capillaries were moderately numerous

The pancreas weighed 100 Gm, and histologically the islets and acini appeared normal

The adrenal glands each weighed 4 Gm, and section revealed no gross fibrosis Histologically the capsule was thickened with fibrous tissue, and all cortical zones were narrowed The cortical cells were filled with fat in small and large droplets The zona reticularis contained moderately coarse, brown pigment and showed no extensive fibrosis The medulla was not appreciably reduced in size and showed the usual cytologic features

The uterus was small and firm, and the endometrium was atrophic and hemorrhagic The tubes were cordlike The ovaries were small and firm Histologically they showed several small cystic spaces, some lined with flattened epithelium, others with cuboidal epithelium which showed papillary projections into the lumen A few cysts contained eosinophilic, homogeneous, acellular material There were several corpora albicantia There were areas of extensive hemorrhage The blood vessels were thickened, and a few were calcified

The brain weighed 1,250 Gm and showed marked sclerosis of the small arteries A thorough study by special neuropathologic methods was not made, and the material is no longer available

COMMENT

The first patient is considered as showing uncomplicated Simmonds' disease.⁵ The differential diagnosis has been well discussed in many of the reports, especially those of Calder,⁶ Silver,⁷ and Gunther and Courville.⁸

Cachexia, which is usually but not always associated with Simmonds' disease, was not present. However, there had been an appreciable loss of weight. It is to be noted that after the preparation of anterior lobe of the hypophysis had been replaced by thyroid the weight fell rapidly. After thyroid was discontinued a high caloric diet was forced. To this the subsequent good nutritional state might be attributed, as cachexia has been prevented by a high carbohydrate intake in experimental animals.⁹ However, Wahlberg¹⁰ noted that after thyroid was given to emaciated patients the loss of weight increased, but when thyroid was discontinued the weight rose far beyond previous levels. Of the patients reported on who showed either no cachexia at death or a gain in weight before death, those of Bratton and Field¹¹ and Aitken and Russell¹² had received thyroid, whereas the patients of Hirsch and Berberich¹³ and Hantschmann,¹⁴ although they had been given a preparation of the anterior lobe of the hypophysis,¹⁵ received no thyroid. Fahr's¹⁶ patient received no glandular therapy. Tauber's¹⁷ patient

5 Simmonds, M. Ueber Kachexie hypophysaren Ursprungs, *Deutsche med Wchnschr* **42** 190, 1916

6 Calder, R. M. Anterior Pituitary Insufficiency (Simmonds' Disease), *Bull Johns Hopkins Hosp* **50** 87 (Feb.) 1932

7 Silver, S. Simmonds' Disease (Cachexia Hypophyseopriva) Report of Case with Postmortem Observations and a Review of the Literature, *Arch Int Med* **51** 175 (Feb.) 1933

8 Gunther, L., and Courville, C. B. Hypophyseal Cachexia (Simmonds' Disease) with Atrophy of Anterior Lobe of Pituitary Gland. Report of Case, *J Nerv & Ment Dis* **82** 40 (July) 1935

9 Mahoney, W. Hypoglycemia Hypophysiopriva, *Am J Physiol* **109** 475 (Sept.) 1934

10 Wahlberg, J. Asthenia Gravis Hypophyseogenea, *Acta med Scandinav* **84** 550, 1935

11 Bratton, A. B., and Field, A. B. Case of Simmonds' Disease, *Lancet* **2** 806 (Oct 13) 1934

12 Aitken, R. S., and Russell, D. S. Case of Simmonds' Syndrome, *Lancet* **2** 802 (Oct 13) 1934

13 Hirsch, S., and Berberich, J. Beitrag zur Frage der multiplen Blutdrüsensklerose (pluriglanduläre Insuffizienz), *Klin Wchnschr* **3** 483, 1924

14 Hantschmann, L. Beitrag zu den Stoffwechselstörungen bei Hypophysenvorderlappenausfall, *Deutsches Arch f klin Med* **176** 397, 1934

15 The preparation used was praephyson

16 Fahr, T. Beitrag zur Pathologie der Hypophyse, *Deutsche med Wchnschr* **44** 206, 1918

17 Tauber, R. L. Zur Kenntnis der Simmondsschen Krankheit, *Med Klin* **23** 1499 (Sept 30) 1927

died of an intercurrent infection, as did the second patient of this report. The explanation which Wahlberg¹⁸ gave for the gain in weight in cases of functional insufficiency of the anterior lobe in which treatment with thyroid was given does not hold in our case, the hypophysis was atrophic beyond the probability of restoration through the relief of one of its functions over a relatively short period. That hypophyseoprivic cachexia is dependent on adrenocortical damage, as suggested by Evans,¹⁹ was not substantiated in this case, the adrenal glands were markedly fibrosed and atrophic, and there was no reason for believing that there was cortical repair during the period in which weight was gained.

The complaint of pain in the joints, which was severe in both the cases here reported, has never been noted as characteristic of Simmonds' disease. It was recorded in the history of each of the patients reported on by Schaefer,²⁰ Hochstetter,²¹ Jakob,²² Graubner,²³ Fink²⁴ and Bratton and Field,¹¹ the ages ranging from 22 to 52 years. The incidence of arthritis in anterior hypophysial insufficiency is, therefore, much lower than that found by Monroe²⁵ in thyroid insufficiency, this suggests that the arthritis may be associated with the secondary involvement of other ductless glands rather than with primary hypophysial insufficiency.

The favorable response to the active principle of the anterior lobe of the hypophysis, which unfortunately was lost sight of when it was discovered that the basal metabolic rate was low, has been frequently reported recently in cases in which a clinical diagnosis of Simmonds' disease was made. No patient for whom this therapy was considered successful has yet been subjected to postmortem examination. The

18 Wahlberg, J. Hypophyseothyrogenic Adiposity and Emaciation, *J A M A* **106** 1968 (June 6) 1936

19 Evans, H. M., Meyer, K., Pencharz, R. I., and Simpson, M. E. Cure of Cachexia Following Hypophysectomy by Administration of Growth Hormone and Its Relation to Resulting Adreno-Cortical Repair, *Science* **75** 442 (April 22) 1932

20 Schaefer, H. Beitrag zur Lehre von den Entzündungen spezifischer und nicht spezifischer Natur in der Hypophyse, Inaug. Dissert., Pathologisches Institut, Jena, 1919, *Centralbl f allg Path u path Anat* **30** 520, 1920

21 Hochstetter, F. Beiträge zur Klinik der multiplen Blutdrüsenklerose, *Med Klin* **18** 661 (May 21) 1922

22 Jakob, A. Zwei Fälle von Simmondscher Krankheit (hypophysäre Kachexie), *Virchows Arch f path Anat* **246** 151, 1923

23 Graubner, W. Die hypophysäre Kachexie (Simmondsche Krankheit), *Ztschr f klin Med* **101** 249, 1925

24 Fink, E. B. Gumma of the Hypophysis and Hypothalamus, *Arch Path* **15** 631 (May) 1933

25 Monroe, R. T. Chronic Arthritis in Hyperthyroidism and Myxedema, *New England J Med* **212** 1074 (June 6) 1935

patients of Simmonds²⁶ and Hirsch and Berberich¹³ showed temporary improvement. A patient with far advanced Simmonds' disease reported on by Weinstein²⁷ did not respond to pituitary substance, and although the patient reported on by Hantschmann¹⁴ appeared to be improving, death from empyema in a month makes evaluation difficult. As Silver⁷ emphasized, there must be a conservative interpretation of the results of substitution therapy in a disease which may have spontaneous remissions and may be of long duration. The 1 cc of a preparation of anterior lobe of the hypophysis once a week given to the patient here reported on seems theoretically inadequate in view of the extensive atrophy of the anterior lobe of the hypophysis. Although Smith²⁸ and Evans¹⁹ have shown that in hypophysectomized rats the atrophic endocrine glands are repaired during hypophysial substitution therapy, there are no reports of the effects of such treatment on atrophic ductless glands which show extensive fibrosis. It seems unlikely that adrenal and thyroid glands that were atrophic and stenosed to the extent seen in the case here reported could adequately respond to the active principle of the anterior lobe of the hypophysis. However, experimental and clinical investigations of this fundamental problem are necessary before any conclusions can be drawn and a rational therapy for Simmonds' disease established.

Extensive studies of the chemical changes in the blood in the episodic or terminal coma of Simmonds' disease have never been reported. Studies such as those made by Loeb²⁹ in adrenal insufficiency would be of great interest. In several cases determinations of the sugar content of the blood have been made, and there was marked hypoglycemia, as was present in our case 1. The extremely low content of chloride in the blood, which unfortunately there was no opportunity to check, is of interest because of the atrophic condition of the adrenal glands, but there was no corresponding hypotension, the blood pressure at the time being 114 systolic and 80 diastolic.

The interesting postmortem observations in this case, aside from those generally reported in Simmonds' disease, were neuropathologic and confirmed those of Jakob,²² who emphasized the importance of changes in the nervous system in Simmonds' disease. The diffuse uncharacteristic changes in the ganglion cells, unassociated with the presence of

26 Simmonds, M. Atrophie des Hypophysenvorderlappens und hypophysäre Kachexie, *Deutsche med. Wchnschr.* **44** 852, 1918.

27 Weinstein, A. Multiglandular Syndromes Resembling Simmonds' Disease, with Case Report, *Am. J. M. Sc.* **189** 245 (Feb.) 1935.

28 Smith, P. E. Hypophysectomy and Replacement Therapy in the Rat, *Am. J. Anat.* **45** 205 (March 30) 1930.

29 Loeb, R. F. Chemical Changes in the Blood in Addison's Disease, *Science* **76** 420 (Nov. 4) 1932.

excessive lipoid pigment or fatty sclerosis, the areas of cellular defects, the protoplasmic growth of the glia cells and the absence of senile plaques and fibrillary degeneration of the nerve cells are identical with his observations. The involvement of the inferior olive, the dentate nucleus of the cerebellum and the corpuscular bodies described by Jakob was not seen. Degenerative products and round cell infiltration around the blood vessels were not noted in Jakob's case but are frequently seen in senile dementia. Otherwise the changes were not similar to those of the senile involutionary process, although definitely of a retrograde or degenerative character. The round cell infiltration represented "symptomatic inflammation" (Spielmeyer) and is not considered an indication of encephalitis. Jakob's observations, which we have confirmed, have apparently not been described by other observers. The changes probably depend on the metabolic disturbances secondary to polyglandular insufficiency and may contribute to the mental symptoms of Simmonds' disease. Jakob observed in a patient with Addison's disease changes like those he described in Simmonds' disease.

In an attempt to determine the significant anatomic changes in the ductless glands in this case of pluriglandular insufficiency, the case was studied in conjunction with one of pluriglandular hyperfunction. The latter was a typical case of acromegaly in a 39 year old man who came to autopsy with a picture in general similar to that reported by Cushing and Davidoff³⁰. The conspicuous difference between Simmonds' disease and acromegaly, apart from size, is the vascularity of the ductless glands. In acromegaly there are numerous thin-walled capillaries adjacent to the glandular units, whereas in Simmonds' disease the capillaries, markedly decreased in number, are usually surrounded by interstitial fibrous tissue. In the thyroid gland (fig 2) the colloid in Simmonds' disease is dense, that in acromegaly is thin and pale, the lining cells of the acini are more cuboidal and contain less fat in acromegaly and there is relatively no fibrous interstitial tissue. The parathyroid glands in acromegaly (fig 3) contain no interstitial adipose tissue and are composed of medium-sized principal cells which border on the pale oxyphilic type, contain little or no lipoid and are arranged in columns, frequently adjacent to large sinusoids containing a thin eosinophilic edema-like substance and capillaries. In neither case is there an appreciable number of definite oxyphilic cells. The parathyroid gland in Simmonds' disease is similar to that described by Jakob²² in his case but does not correspond in detail to the type described by Houssay³¹ after hypophysectomy in animals,

30 Cushing, H., and Davidoff, L. M. The Pathological Findings in Four Autopsied Cases of Acromegaly, with a Discussion of Their Significance, Monograph 22, Rockefeller Institute for Medical Research, April 23, 1927.

31 Houssay, B. A. Certain Relations Between the Parathyroid, the Hypophysis and the Pancreas, *New England J. Med.* **214** 1128 (June 4) 1936.

nor does the parathyroid gland in acromegaly have the same structure as that briefly described by him in induced hyperpituitarism in animals. In routine sections of the pancreas stained with hematoxylin and eosin and with stains for fat, the islets of Langerhans appear to be made up of similar cells, which in acromegaly have slightly more cytoplasm but are not more numerous. The fibrosis noted in other glands in Simmonds' disease is not present in the pancreas. In the adrenal glands there is a great difference (fig 4). The zona reticularis in Simmonds' disease (our case 1) is fibrous, and only a rare shrunken pigmented cell remains, this contrasts markedly with the wide zona reticularis in the case of acromegaly in which the cells were large and laden with pigment. The lipid, which is extensively deposited throughout the adrenal gland in Simmonds' disease, is present chiefly in the zona glomerulosa and in the peripheral third of the zona fasciculata in the adrenal gland in acromegaly. Although the adrenal glands in this particular case of Simmonds' disease did not correspond to any of the types described by Zwemer,³² those of the acromegalic patient corresponded in most respects to his type of "severe exhaustion of the adrenal."

The second patient here reported on may be classed as having Simmonds' disease but dying of intercurrent infection, the history and symptoms were those of both conditions, and the effect of this interrelationship is difficult to evaluate. Periods of fever and mental disturbances have been previously reported in Simmonds' disease.²⁷ Whether cachexia and microsplanchnia would have developed had the patient not succumbed to an intercurrent infection is impossible to determine. The only anatomic feature by which the diagnosis of Simmonds' disease may be justified is atrophy of the pituitary out of proportion to the general glandular atrophy.

SUMMARY

Two patients with Simmonds' disease are reported on. The first patient showed the typical postmortem picture of fibrosis and almost complete atrophy of the anterior lobe of the hypophysis, fibrosis and marked atrophy of the adrenal glands, thyroid glands and gonads, as well as visceral microsplanchnia. The patient showed the characteristic history of onset following a complicated pregnancy and the loss of hair, teeth and sexual functions, and symptoms of weakness, chilliness and poor appetite, together with a subnormal temperature, a low basal metabolic rate, an increased sugar tolerance and anemia and a fatal termination in hypoglycemic coma. The lack of cachexia was explained as a result possibly of therapy. The central nervous system showed an uncharacteristic diffuse disease of the ganglion and glia cells and cellular

³² Zwemer, R. L. Study of Adrenal Cortex Morphology, *Am J Path* **12** 107 (Jan) 1936

defects in the cortex, changes which confirmed the observations of Jakob. The nucleus supra-opticus exhibited loss and degeneration of the ganglion cells.

The second patient presented several characteristics of Simmonds' disease—the onset of the menopause following toxemia of pregnancy, fatigue, mental disturbances, scanty body hair, a low basal metabolic rate and at autopsy an almost completely atrophic anterior lobe of the hypophysis and moderately atrophic adrenal and thyroid glands, but cachexia had never developed, death was not in hypoglycemic coma and there was no visceral microsplachnia. The additional history of episodes of chills and fever and the finding of chronic and acute cystitis and pyelonephritis suggested that this intercurrent infection rather than Simmonds' disease was the terminating factor.

In both cases pain in the knees was a prominent symptom.

A REVIEW OF FOUR HUNDRED AND FORTY CASES OF PELLAGRA

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AND

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AUGUSTA, GA

From a clinical standpoint the problems of the etiology and treatment of pellagra remain unsolved, and the mortality rates in general hospitals range between 20 and 50 per cent. In an effort to determine the most promising fields for further inquiry into the etiology of pellagra and also to determine the causes of such persistently high death rates, the records of 440 patients with this disease were analyzed. When patients were admitted to the hospital more than once, the new data were added to those previously recorded, no patient was counted twice. The interval over which the observations were made covered the sixteen years between Jan 1, 1919, and Dec 31, 1934.

Several reviews of pellagra have appeared during recent years, notably those of Turner,¹ Boggs and Padget,² Mulholland and King³ and Garrett.⁴ It was felt that our series, being considerably larger than those previously reviewed and representing patients drawn from a relatively small community which has perhaps undergone less economic stress during the past decade than larger centers of population, might throw added light on the problem.

The diagnosis was based on the usual criteria of stomatitis with glossitis, dermatitis of characteristic type, diarrhea and psychoses. The diagnosis was not considered established unless at least two of these conditions were present. In many instances typical glossitis and dermatitis were considered adequate.

As shown in chart 1, there was a marked increase in pellagra after 1924, the peak being reached in 1929, with sharp declines in 1930

From the University of Georgia School of Medicine, and the University Hospital

1 Turner, R H. Pathologic Physiology of Pellagra. Tabulated Clinical and Physiological Data, *J Clin Investigation* **10** 61-70 (April) 1931

2 Boggs, T R, and Padget, P. Pellagra. Analysis of One Hundred and Two Cases, *Bull Johns Hopkins Hosp* **50** 21-32 (Jan) 1932

3 Mulholland, H B, and King, R L. Pellagra. Review of Cases with Special Reference to Gastric Secretions, *J A M A* **101** 576-580 (Aug 19) 1933

4 Garrett, T C. Analysis of Cases of Pellagra Admitted to Pennsylvania Hospital Since 1922, *Am J M Sc* **190** 525-535 (Oct) 1935

and 1934. No adequate explanation has been offered for the increase in 1929. This was a period of relative prosperity and great industrial activity in the community, few persons were unemployed and the general scale of living was perhaps at an all time high level in all classes of the population. Alcoholism was not a factor.

Chart 2 shows the incidence of pellagra by months. There was the usual seasonal distribution, the greatest number of patients being admitted during the early summer. As the average duration of symptoms prior to hospitalization was four weeks, the July peak therefore represented cases beginning in May and June. However, pellagra occurred throughout the year.

Of the 440 patients, 250 were white patients and 190 were Negroes, all from a population almost exactly divided between the races. Of the white patients, 88 (35.2 per cent) were males and 162 (64.8 per

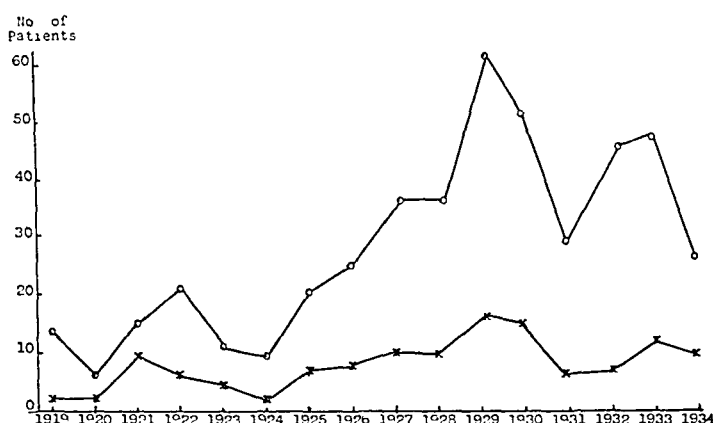


Chart 1—The incidence (upper line) and the mortality (lower line) of pellagra

cent) were females. Of the Negroes, 56 (29.5 per cent) were males and 134 (70.5 per cent) were females.

The age distribution was wide, patients of all ages between 5 and 89 years being observed. The ages of over half (285) fell into the three decades between 21 and 50 years, inclusive.

The death rate showed differences, possibly of significance, as to race and sex. Of the white males, 22 (25 per cent) died, of the white females, 33 (20.4 per cent) died. The total mortality among the white patients was 22.7 per cent. Of the Negroes, 28.5 per cent of the males and 35.8 per cent of the females did not recover. The total mortality among Negroes was 33.7 per cent (chart 3). The effect of yeast therapy was probably reflected in the death rate. During the seven years between 1919 and 1925, 92 patients were treated with a high protein, high caloric diet, with the addition of citrus fruit juice, milk, cod liver oil and diluted hydrochloric acid. Many were fed by tube to insure adequate nourishment, and a large number were given arsenic in various

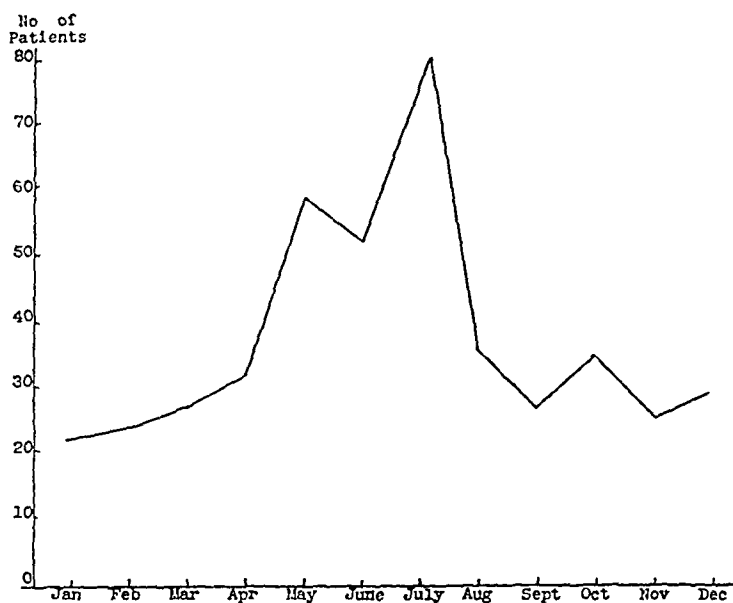


Chart 2—The incidence of pellagra by months

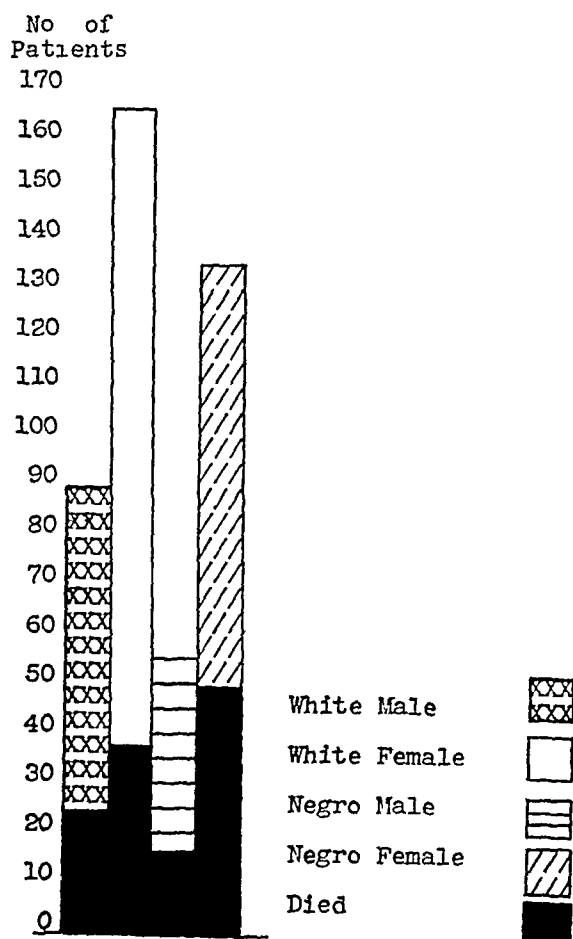


Chart 3—The incidence and mortality rate of pellagra by race and sex

forms This group of patients showed a 33.7 per cent mortality. During January 1926, at Dr. Goldberger's suggestion, dried yeast was added to the diet in amounts varying between 30 and 90 Gm daily, and all empirical medication was discontinued. During the ensuing nine years 348 patients were treated, 88 (25.3 per cent) of whom died, the favorable differential under yeast treatment was therefore 84 per cent. The total percentage of deaths during the entire period was 27.04 per cent. The largest number of deaths occurred among patients in the age group from 31 to 50, and the actual rate of mortality increased sharply after the fourth decade (chart 4).

The occurrence of "cardinal" symptoms and signs and their apparent relation to the fatal outcomes is shown in table 1. No very significant differences were present, except in the incidence of psychoses, these were noted nearly twice as frequently in the fatal cases.

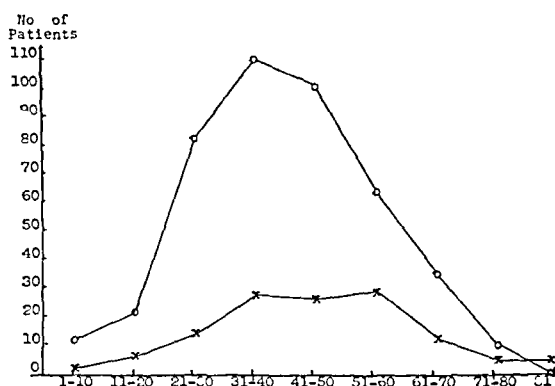


Chart 4—The age incidence (indicated by o's) and the mortality rate (indicated by x's) by decades.

The incidence of fever was studied on account of the widely held opinion that a persistent or marked elevation of temperature without definite infection carries a bad prognosis. Complications which were considered adequate cause for fever occurred in 68 patients (table 4), among the remainder of the group temperatures exceeding 99.5 F were recorded over periods of not less than five days in 222 instances. High fever was seen almost exclusively among those who died. The relative distribution of pyrexia is shown in table 2.

Considerable importance was attached to examinations of the blood. Estimations of the sugar and nonprotein nitrogen contents of the blood were made 420 times, and nothing of significance was observed. Hemoglobin determinations by Sahli's method and erythrocyte and leukocyte counts were obtained for all but a few patients. Anemia was considered present when the hemoglobin value was below 80 per cent and the red cell count below 4,000,000. In certain instances anemia was certainly masked by dehydration, usually in the most severely ill patients,

for many of whom only one examination of the blood was made. Anemia was present in 83.6 per cent of the patients, in 22 patients (5 per cent) the color index exceeded 1.1, and the anemia was classed

TABLE 1—*Distribution of Cardinal Signs and Symptoms*

	Patients Who Recovered (321)	Percentage	Patients Who Died (119)	Percentage	Total Number of Patients	Percentage of Entire Group
Glossitis and stomatitis	310	96.5	117	98.3	427	97.04
Dermatitis	299	93.1	117	98.3	416	94.50
Diarrhea	220	68.5	91	76.5	311	70.70
Psychoses	130	40.5	91	76.5	221	50.20

TABLE 2—*Range of Temperature*

	Temperature, F				Total
	99.6-101	101-102	102-103	103-106	
Patients who recovered	86	15	8	3	112
Patients who died	36	14	10	50	110
Totals	122	29	18	53	222

TABLE 3—*Results of Examinations of the Blood*

	Hemoglobin, %						Total
	20-29	30-39	40-49	50-59	60-69	70-79	
Patients who recovered	3	3	20	42	84	110	319
Patients who died	3	6	11	22	21	33	114
Totals	6	9	31	64	105	143	433

	Erythrocytes, Millions						Total
	1-1.4	1.5-1.9	2-2.4	2.5-2.9	3-3.4	3.5-3.9	
Patients who recovered	1	1	12	29	66	78	321
Patients who died	1	4	9	10	21	22	118
Totals	2	5	21	39	87	100	439

	Leukocytes, Thousands				Total
	Below 5	5-7.4	7.5-9.9	10-12.4	
Patients who recovered	29	96	121	48	318
Patients who died	12	40	27	10	113
Totals	41	136	148	58	481

as hyperchromic (unfortunately, the volume index was not determined for these patients). The remaining 77.6 per cent of the group definitely showed hypochromic anemia. The leukocyte counts were of no special significance, counts above 7,400 being recorded 254 times. The degree and distribution of anemia and of leukopenia and leukocytosis are shown in table 3.

The gastric content in its relation to adequate gastric function is a matter of much interest and possible importance. In this series only 247 patients had test meals, as the importance of this procedure was not appreciated during the earlier years. The Ewald meal was used, and in most instances the fractional method of withdrawal was practiced, histamine was not used. It was noted that the amount of the contents recovered after a test meal was almost uniformly small, seldom exceeding 50 cc. In patients with apparent anacidity the late appearance of

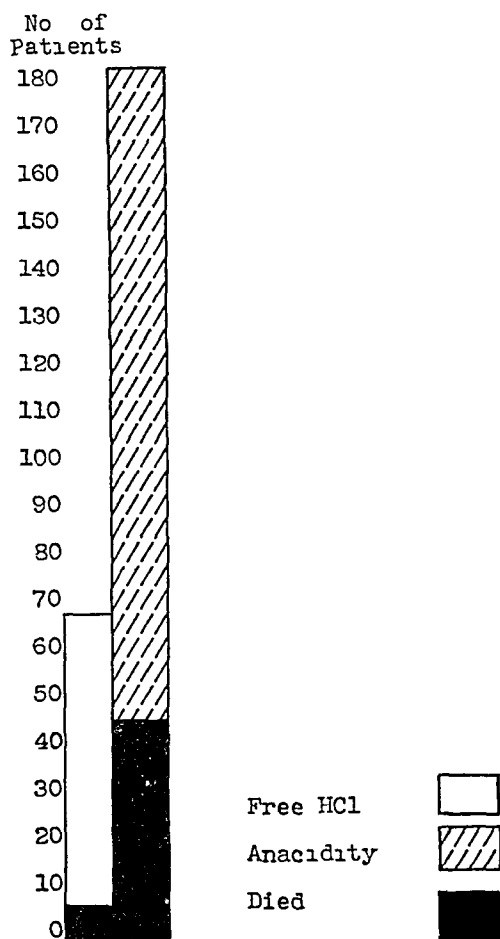


Chart 5—The relation between gastric acidity and the mortality rate

free acid was not noted. In 67 patients there was some free hydrochloric acid, 6 of these patients died, giving a mortality rate of 8.9 per cent. Achlorhydria was shown by 180, 43 (23.9 per cent) of whom did not recover. Seventy (38.9 per cent) of the 193 patients whose gastric content was not examined succumbed. The apparent relation of achlorhydria to the mortality rate is shown in chart 5.

Neurologic disturbances other than psychoses were not frequent, and in this respect our series varied widely from those reported by others.

Some evidences of combined sclerosis were noted in 33 patients (75 per cent) and peripheral neuritis in only 11 patients (25 per cent). The very low incidence of peripheral neuritis may possibly be accounted for by the relative rarity of alcoholism among our patients.

Alcohol as a causative or precipitating factor of pellagra had no influence comparable to that noted in the experience of Boggs and

TABLE 4—*Complications*

Disease	Number of Patients	Patients Who Recovered	Patients Who Died
Amebiasis	3	3	0
Arteriosclerosis	10	8	2
Arthritis, chronic	2	1	1
Asthma	3	3	0
Bronchopneumonia	25	2	23
Cerebral hemorrhage	2	1	1
Granuloma venereum	2	2	0
Heart disease (all types)	30	22	8
Helminthiasis	5	5	0
Hypertension (essential)	7	5	2
Hyperthyroidism	1	1	0
Malaria	4	4	0
Meningitis (septic)	1	0	1
Morphinism	2	2	0
Nephritis (all types)	4	1	3
Obesity	1	1	0
Otitis media, acute	1	0	1
Pelvic inflammation	14	11	3
Pneumonia, lobar	2	0	2
Pulmonary abscess	1	0	1
Starvation	4	0	4
Syphilis (all stages)	57	42	15
Tuberculosis	18	12	6
Urinary infections	13	13	0

TABLE 5—*Relation of Recovery to Extent of Hospitalization*

Days in Hospital	Patients Who Recovered	Patients Who Died
1-7	24	54
8-14	73	34
15-21	86	13
22-28	39	5
29-35	31	2
36-42	22	5
43-49	14	2
50-56	5	2
57-63	9	0
64 and over	18	2

Padgett² or of Spies and DeWolf.⁵ A history of severe acute or chronic alcoholism was obtained for only 38 patients (88 per cent). In practically every instance it was felt that it did have a direct bearing on the development of pellagra. In the great majority there had been a tremendous consumption of unaged illicitly distilled corn whisky over a relatively short period, varying from two to eight weeks prior to the

5 Spies, T. D., and DeWolf, H. F. Observations on the Etiologic Relationship of Severe Alcoholism to Pellagra, *Am J M Sc* **186** 521-525 (Oct) 1933

onset of symptoms The occurrence of peripheral neuritis was much more frequent in the group of alcoholic patients (8 of the 11 instances) The mortality rate was not influenced by alcohol—8 of the 38 alcoholic patients died

Complications were recognized in 215 patients, and their nature and relation to the mortality are shown in table 4 Severe acute pulmonary infection, heart disease and possibly syphilis were the only concurrent ailments which seemed to have a definite influence on the outcome

As a matter of interest the relation of recovery to the duration of hospitalization was noted It is significant that 45.4 per cent of the deaths occurred during the first week of hospitalization and 73.7 per cent during the first two weeks These patients showed an advanced, dehydrated and usually febrile condition and were profoundly demented, not being amenable to any form of therapy yet suggested The data are presented in table 5

COMMENT AND CONCLUSIONS

The items of possible significance which appear in this analysis are few but rather well defined The relatively high death rate among Negroes is difficult of explanation Syphilis and tuberculosis are more common among them than among white persons, but these diseases do not account for more than a small fraction of the difference in mortality Contrary to the general impression, the southern Negro lives well, and while his diet may be somewhat low in proteins of optimum biologic value, it is rich in green vegetables of good vitamin B₂ content Neglect of symptoms cannot be considered the cause, as the Negro population from which these patients were drawn has been the object of almost paternal medical supervision for about a century, and medical advice is sought by them for the most trivial complaints

The incidence of lesions of the spinal cord and of peripheral neuritis was notably less among our patients than that noted in other reports, on the other hand, psychoses attributable to pellagra were considerably more frequent It is possible that these conditions depend on the factors precipitating the syndrome When alcoholism is important, lesions of the peripheral nerves seem to be much more frequent

Alcohol as an apparent etiologic factor was almost negligible in this group, but that it may be a potent cause of pellagra is not denied It is well known that the gastric function is greatly impaired by severe alcoholism, and this we believe to be of greater importance than any inadequate intake of food during a spree

Anemia occurred frequently, but in the great majority of patients it was definitely hypochromic A few patients who showed a color index greater than unity were not controlled by determinations of the volume index Studies of the bone marrow of a small number of patients

with severe pellagra indicated that its reaction is definitely nonspecific⁶ These observations are in accord with those of other authors

The importance of gastric dysfunction and possibly of hepatic changes has not been generally emphasized Mulholland and King³ discounted it, Boggs and Padget² and Spies and Payne⁷ have stressed it We have been particularly impressed by the frequency of anacidity and by the inadequate amounts of gastric contents recovered from pellagrins even when free hydrochloric acid was present Helmer, Fouts and Zerfas⁸ have shown that the pepsin and rennin contents are diminished in the gastric mucosa of patients with pellagra That a grave defect of gastric function exists seems most likely, and experiments carried out in this clinic suggest that it is the determining factor in the production of the syndrome⁹ Lesions of the liver, most often fatty degeneration, are present in a great majority of the patients coming to necropsy (92 per cent of our small series) These have been noted by all observers, but their significance has been discounted It seems likely that they may have great importance as part of a picture of gastro-intestinal failure Levin¹⁰ has expressed the opinion that the liver controls the acid production of the stomach That the changes in the gastro-intestinal function are primary and causative rather than secondary to pellagra is an attractive hypothesis Further, it seems probable that these changes result in an intrinsic deficiency analogous to but probably distinct from that which is present in pernicious anemia

6 Krjukoff, A Blut und Blutbildung bei schweren Fallen von Pellagra, *Folia haemat* **45** 196-206 (Sept) 1931 Vryonis, G P Unpublished observations

7 Spies, T D, and Payne, W A Study of the Etiologic Relationship Between Pellagra and Pernicious Anemia, *J Clin Investigation* **12** 229-234 (Jan) 1934

8 Helmer, O M, Fouts, P J, and Zerfas, L G Gastro-Intestinal Studies III Determinations of Enzymes on Autopsy Specimens from Cases of Pernicious Anemia and Pellagra, *Arch Int Med* **53** 675-679 (May) 1934

9 Sydenstricker, V P, Armstrong, E S, Derrick, C J, and Kemp, P S On the Existence of an Intrinsic Deficiency in Pellagra, *Am J M Sc* **192** 1-8, (July) 1936 Sydenstricker, V P, and Kemp, P S Unpublished observations

10 Levin, A L, in discussion on Mulholland and King³

Progress in Internal Medicine

DISEASES OF THE HEART

A REVIEW OF SOME CONTRIBUTIONS MADE DURING 1936

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The suggestion that foreign medical reports be given greater emphasis than heretofore seems worth while, because of the fact that they are less readily available to the average reader. Accordingly, the review this year assumes a more international character. The material has again been organized very simply, with the etiologic subdivisions made as complete as possible. For example, under the heading "Rheumatic Heart Disease" will be found nearly all the material specifically relating to this illness. No attempt has been made to review the various textbooks and monographs, as this has already been done adequately.

PHYSIOLOGY AND EXPERIMENTAL PATHOLOGY

Investigation of the action of the vagus and sympathetic nerves or of their chemical mediators on the heart is being vigorously pushed¹

In an effort better to understand the factors controlling cardiac acceleration during muscular exercise, Brouha, Cannon and Dill^{1a} made a series of extremely interesting experiments on totally sympathectomized dogs. Before sympathectomy the average heart rate during rest is around 110 beats a minute, after an emotional stimulus the heart rate may jump to from 180 to 220, during light exercise the rate ranges from 170 to 200, during average exercise the rate stabilizes around 220 to 240, during intense exercise the rate often reaches 240 to 260 in the first six seconds, and, as exercise is prolonged, it

From the Cardiac Clinic of the Massachusetts General Hospital

1 (a) Brouha, L., Cannon, W. B., and Dill, D. B. The Heart Rate of the Sympathectomized Dog in Rest and Exercise, *J. Physiol.* **87** 345, 1936. (b) Pinkston, J. O., Partington, P. F., and Rosenblueth, A. A Further Study of Reflex Changes of Blood Pressure in Completely Sympathectomized Animals, *Am. J. Physiol.* **115** 711, 1936. (c) Gremels, Hans. Ueber die Steuerung der energetischen Vorgänge am Säugetierherzen, *Arch. f. exper. Path. u. Pharmacol.* **182** 1, 1936. (d) Bronk, D. W., Ferguson, L. K., Margaria, R., and Solandt, D. Y. The Activity of the Cardiac Sympathetic Centers, *Am. J. Physiol.* **117** 237, 1936.

may reach 300 to 315. The cardiac deceleration following exercise is not always the same after comparable amounts of exercise, although it drops markedly within six seconds after average or intense exercise.

After total sympathectomy the heart rate averages around 82 beats a minute, which is definitely below that for normal dogs. Respiratory arrhythmia is always more marked than normal. An emotional stimulus always produces cardiac acceleration, and the rate may jump from 80 to 140 or even 180 beats a minute, during light exercise it stabilizes between 120 and 140 and during average exercise between 160 and 200, during intense exercise following a sudden initial acceleration there is a progressive rise to 200 or more. Cardiac deceleration follows the normal pattern.

Three months after operation the heart rate remains slow, but the capacity for work is about normal, exercise is accomplished without effort, muscular coordination is faultless, and the animals are not short of breath and show normal fatigability. The sugar and lactic acid content of the blood, the alkali reserve and the body temperature vary within normal limits.

The explanation of this cardiac acceleration in totally sympathectomized dogs, which is only 30 or 40 per cent below normal, was not found in a change of body temperature, the action of muscular metabolites or the liberation of epinephrine or sympathin. They did find that when atropine was injected the heart rate reached from 210 to 230 beats a minute. The same dose of atropine after section of both vagus nerves produced no effect, the rate stabilizing around 130 beats a minute, but stimulation of the peripheral ends of both vagus nerves resulted in cardiac acceleration, which in one dog reached 230 beats a minute. The authors concluded from this that bilateral vagotomy suppresses some accelerator mechanism which comes into play during exercise or under the influence of atropine. This mechanism is not seen in cats, but it is probably present in man. The important researches of Jourdan and Nowak are mentioned, wherein they demonstrated in dogs the existence of cardio-accelerator fibers coming from the mesencephalon, leaving the brain by way of the vagus nerve and going down to the vagosympathetic trunk. The same authors have shown that these fibers are put into action during asphyxia.

Anrep, Barsoum and Talaat² have shown that the cardiac muscle in the heart-lung preparation of a dog continuously produces measurable quantities of a histamine-like substance. The behavior of this substance in the presence of various chemical reagents and the manner in which

² Anrep, G. V., Barsoum, G. S., and Talaat, M. Liberation of Histamine by the Heart Muscle, *J. Physiol.* **86** 431, 1936.

it acts on various biologic test objects provide strong evidence that this substance is actually histamine. The production of histamine is increased by raising the blood pressure and to a much greater extent by the administration of epinephrine. In every instance of increased production of histamine there is also an increase of its concentration in the blood of the coronary veins, which suggests the possibility that histamine may participate in the augmentation of coronary blood flow observed when the arterial blood pressure is raised. The important question is raised as to whether the epinephrine acts as a coronary vasodilator by direct action on the sympathetic nerve endings or through the liberation of a metabolite, possibly histamine. Further experimentation is necessary to decide this question. The observation that an excess of carbon dioxide and especially a deficiency in oxygen also cause a conspicuous increase in the production of histamine suggests that this increase may be indirectly due to relative anoxemia or a change in the acid-base equilibrium within the contracting muscle cell.

Radnai and Ascher³ have made an interesting contribution concerning the compensatory increase in the size of the cardiac valves. The study was actually begun by Radnai in 1929 with the development of a method accurately to determine the surface area of cardiac valves. In the course of his early investigations it appeared that in those cases of syphilitic aortitis and to a lesser degree in arteriosclerosis in which the process was not extended over the aortic valve, this valve was considerably enlarged. Furthermore, it appeared that this valvular enlargement was often of a higher degree than the enlargement of the aortic opening. In certain instances the valve could completely close an aortic opening twice or more than twice normal size. Consequently, relative aortic insufficiency is found uncommonly not because of "rigidity" of the aortic opening but because the dilated opening can be closed by the enlarged healthy aortic valve.

It was only natural to extend this study to the investigation of other cardiac valves. Radnai and Ascher showed that in normal subjects the area of the pulmonary valve is slightly larger than that of the aortic valve. In instances of pulmonary hypertension the pulmonary valve is strikingly enlarged not only in relation to the normal but also in comparison with the normal aortic valve of the same subject. The increase in size of the pulmonary valve stands in close relationship to the degree of hypertrophy of the right ventricle and is similar in degree whether the increase in blood pressure in the pulmonary artery is due to mitral stenosis or to severe emphysema. Enlargement of the

3 Radnai, P, and Ascher, F. Ueber die kompensierende Vergrosserung der Herzklappen, *Deutsches Arch f klin Med* **179** 142, 1936

pulmonary valve contrasts with that of the aortic valve in that there is a smaller difference between the area of the valve and the size of the opening. Thus there is not the far-reaching protection against the development of relative insufficiency of the pulmonary valve that there is against aortic insufficiency. This discrepancy between the enlargement of the pulmonary and that of the aortic valve is shown in all probability to be due to the different forces at work. In the case of the former, the chief factor is the increase in blood pressure, while in the latter case the chief factor lies in the disease of the aortic wall, which permits the downward displacement of the sinus of Valsalva.

Radnai and Ascher next considered whether this mechanism of compensatory enlargement applies to the mitral valve. The accompanying tabulation summarizes their results:

	Average Value, Sq Mm	Maximal Value, Sq Mm	Minimal Value, Sq Mm
Area of mitral valve in normal subjects	1,573	2,170	1,000
Area of mitral valve in subjects with hypertrophy of left ventricle	1,850	3,000	1,100

The probable mechanism of enlargement of the mitral valve is considered. Because this enlargement is relatively slight, compared with the dilatation of the mitral orifice in instances of hypertrophy of the left ventricle, mitral insufficiency is of common occurrence.

Dieckhoff⁴ has pointed out that it has long been known that the hypertrophied heart of a patient in congestive failure is more sensitive to digitalis than is a normal heart. Corresponding experiments on animals have confirmed this observation, and Dieckhoff decided to determine whether the presence of hypertrophy without decompensation is associated with an increase in sensitivity to digitalis. The tests were carried out on cats in which the left ventricle was markedly hypertrophied as a result of artificially produced aortic insufficiency. It was found that the sensitivity to digitoxin and strophanthin was definitely increased, whereas it was normal in hearts with recently produced aortic insufficiency without hypertrophy.

In a further study Dieckhoff⁵ performed an interesting series of experiments on cats' hearts, using Starling's heart-lung preparation. When aortic insufficiency is produced by injuring a single cusp of a valve, the ability of the heart to do work is markedly reduced below normal, whereas if the valvular injury is of long standing (one hundred

4 Dieckhoff, J. Digitoxin-Strophanthin-Empfindlichkeit aortenklappeninsuffizienter Herzen mit und ohne Hypertrophie, *Arch f exper Path u Pharmakol* **182** 285, 1936.

5 Dieckhoff, J. Leistungsfähigkeit aortenklappeninsuffizienter Herzen ohne und mit Hypertrophie im Herz-Lungen-Präparat (nebst Digitalisierungseffekten), *Arch f exper Path u Pharmakol* **182** 268, 1936.

to one hundred and fifty-four days) and accompanied with cardiac hypertrophy, the ability to do work approaches that of a normal heart. After injury to two aortic cusps the ability of the heart to do work is severely reduced, and this ability is not appreciably raised, even after passive hypertrophy. It was found that a heart with a fresh defect of the aortic valve which was made functionally complete by means of an ingenious artificial valve behaved similarly to a normal heart-lung preparation. If a heart that was hypertrophied as a result of long-standing valvular injury was made functionally complete by means of an artificial valve, it was capable of more work than a normal heart.

Other papers on physiology and experimental pathology⁶ cannot be mentioned in detail, because of considerations of space.

ROENTGENOLOGY

The exhibition last year of excellent cineroentgenograms aroused great interest. Progress in cineroentgenography has been slow because of many serious difficulties.⁷ The fundamental difficulty lies in the fact that x-rays will not refract in the manner of light rays, thereby making it impossible to focus them on a photographic film. Consequently it is necessary either to use a film of sufficient dimension to contain a natural-sized image of the object to be pictured or to photograph the image produced on a fluorescent screen. The former, so-called direct, method is being utilized by van de Maele and by others, while the latter, or indirect, method is being used by Djian,⁸ by Reynolds and by Jankei. Reynolds⁷ has described his experiments and the many improvements in apparatus and technic made from time to time which have at last made indirect cineroentgenography a really practical achievement. At present it is impossible correctly to evaluate the many and far-reaching potentialities of this procedure. It should prove of immense value in the functional study of a moving, irregular, three-dimensional organ such as the heart.

6 Green, H. D. The Coronary Blood Flow in Aortic Stenosis, in Aortic Insufficiency and in Arterio-Venous Fistula, *Am J Physiol* **115** 94, 1936. Gauer, O. Ueber Pulswellengeschwindigkeit in Aorta und Beinarterien des Menschen, *Ztschr f Kreislaufforsch* **28** 7, 1936. Haynes, F. W., Ellis, L. B., and Weiss, S. Pulse Wave Velocity and Arterial Elasticity in Arterial Hypertension, Arteriosclerosis, and Related Conditions, *Am Heart J* **11** 385, 1936. Rothberger, C. J. and Zwilling, L. Ueber die Wirkung von Magnesium auf die Strophanthin- und die Barium-Tachykardie, *Arch f exper Path u Pharmacol* **181** 301, 1936. Bay, E. B. The Work of the Left Ventricle in Aortic Insufficiency, *J Clin Investigation* **15** 643, 1936.

7 Reynolds, R. J. Cineradiography, *Fortschr a d Geb d Rontgenstrahlen* **53** 602, 1936.

8 A copy of Djian's cineroentgenogram of the heart was demonstrated by H. B. Sprague before a small group of physicians in Boston.

Four years of study and experimentation with roentgenkymography⁹ have confirmed some of the early enthusiasm regarding its use in cardiovascular disorders. It is an objective and accurate method for graphically recording the physiologic and pathologic movements of the heart and great vessels, and its usefulness includes accurate topographic identification of the cardiac chambers, additional aid in the diagnosis of certain diseases of the heart, pericardium and great vessels, and better evaluation of the tonicity and force of contraction of the left ventricle.

Faber and Kjaergaard,^{9f} in an excellent article, have pointed out that there have long been published several experimental roentgenologic works on the function of the heart which seem to unsettle somehow the conceptions adopted by the physiologists. According to Starling, the increased influx of venous blood during diastole produces temporarily a dilatation of the ventricles of the heart, so that the muscle fibers are lengthened prior to systolic contraction. This has been termed the physiologic dilatation of the heart, and many physiologists subscribe to this theory. During the past thirty-four years the results of numerous roentgenographic studies of the working heart have been incompatible with this theory. These studies have shown that in healthy persons there is usually a reduction in the size of the heart immediately after exercise. Occasionally there were found to be slight increases in size, but any considerable dilatation of the heart after maximal exertion occurs only when the myocardium is seriously affected.

The authors just mentioned made kymographic examinations of the hearts of 50 healthy young subjects during brief severe work. It was found that brief work produces changes in the heart similar to those that are demonstrable after more protracted work. These are increase of the rate of the beat and increase in the power of the individual contractions, associated with a rise of the blood pressure and a diminution in size of the heart both in systole and in diastole. The amplitude of excursion of the left ventricle increases significantly, and the same is true in a lesser degree for the right ventricle, which presumably accounts for the increased beat volume.

9 (a) Heier, H. Herzwandveränderungen im Flächenkymogramm, *Fortschr a d Geb d Rontgenstrahlen* **53** 895, 1936. (b) Delherm, L., and Fischgold, H. Quatre années de radiokymographie cardiovasculaire, *ibid* **53** 223, 1936. (c) Scott, W. G., and Moore, S. The Construction of Roentgenkymographs and Kymoscopes, *Radiology* **26** 622, 1936. (d) Roentgenkymography in Diseases of the Heart. A Relatively New and Efficient Aid in Diagnosis, *J A M A* **107** 1951 (Dec 12). (e) Hirsch, I. S., and Gubner, R. Application of Roentgenkymography to the Study of Normal and Abnormal Cardiac Physiology, *Am Heart J* **12** 413, 1936. (f) Faber, B., and Kjaergaard, H. Kymographic Studies on the Influence of Brief Muscular Work upon the Heart Function, *Acta med Scandinav* **89** 537, 1936.

It is evident from this and other studies that the increase of the beat volume in the working heart cannot be due to the increased diastolic dilatation but that it is due to an increased emptying power and a decrease in the volume of the heart during rest. The idea of passive dilatation of the heart as a cause of the increased minute volume is therefore, in the authors' opinion, to be replaced by a more active conception of the compensatory power of the heart and the increased beat volume.

Evans¹⁰ has written the best account in the English language of the course of the esophagus in health and in disease of the heart and great vessels. The natural pliancy and intimate relationship of the esophagus to the heart and great vessels explains how readily its course may be altered by disease in these structures. These alterations together with the roentgenographic anatomy of the normal esophagus have been well described. It is our object to present this work in sufficient detail to be of practical value, unfortunately, it is not feasible to reproduce the illustrations.

A marmalade-flavored suspension of barium sulfate and another palatable preparation of barium sulfate were found especially suitable opaque meal substances. The position of choice for roentgenoscopy, with due regard to practicability, was found to be with the patient's arm raised and the hand placed on the head. Examination was always carried out in the three conventional positions—anterior, right oblique and left oblique.

Four esophageal curves or impressions can be seen in the healthy subject, and according to the viscus producing them, they have been designated as the impressions of the aortic arch, the left bronchus, the left aortic arch and the descending aorta. An impression caused by the left ventricle can sometimes be seen in the left oblique position. The contour of each curve alters when the patient is rotated to the right or to the left, and there is an optimal point at which each curve can be portrayed.

The impression of the aortic arch is produced by that portion of the arch which has commenced to descend. The concavity of the curve is directed to the left, is about 3 cm. long and, although seen in all three positions, is best seen in the anterior and in the right oblique position. Evans constructively criticizes Kieuzfuchs' method of determining the diameter of the aortic arch (distance from the aortic impression to the opposite border of the aortic shadow) by discussing variables which sometimes invalidate it.

¹⁰ Evans, W. The Course of the Oesophagus in Health, and in Disease of the Heart and Great Vessels, Medical Research Council, Special Report Series, no. 208, London, His Majesty's Stationery Office, 1936.

In congenital dextrocardia the concavity of the impression of the aortic arch is directed toward the right and the other esophageal impressions also are reversed. In dextroposition of the aorta in the absence of dextrocardia, the impression of the aortic arch is directed toward the right, but the remaining esophageal impressions are unaltered.

In syphilitic aortitis the impression of the aortic arch may be displaced and elongated, and the diameter of the aorta may be increased. Changes limited to the ascending aorta or to the first portion of the aortic arch seldom disturb the impression. If the displacement is well marked and to the right in the anterior position, the aortic dilatation has occurred in the descending portion of the arch and chiefly to the right. If the impression is elongated without displacement and the aortic prominence is mostly to the left, the aortitis is situated in the descending portion of the arch and the upper part of the descending aorta. The effects of atheroma and hypertension on the impression of the aortic arch must be excluded before the changes are attributed to aortitis.

The impression of the aortic arch is clearly seen in all three positions and often is elongated in the anterior position if atheroma of the aorta is present. The dense aortic shadow in relation to the curve of the barium appears like a ball in a socket.

Deformity of the impression of the aortic arch may be produced by carcinomatous bronchial glands, goiter, aneurysm of the innominate artery and other conditions.

The impression of the left bronchus on the esophagus commences immediately below the impression of the aortic arch and is from 2 to 3 cm long. It is poorly seen in the anterior position and best seen in the right oblique position, where the concavity of the curve is in the same direction as the impression of the aortic arch; in the left oblique position the concavity of the curve is oppositely directed to the impression of the aortic arch. Alteration of the curve of the left bronchus is not a frequent finding in cardiovascular disease, because of the rigidity of the bronchus which produces the impression. Accentuation of the curve may result from mitral stenosis but not from enlargement of the pulmonary artery. The impression of the left bronchus is the curve of least clinical importance.

In normal persons the impression of the left auricle is usually visible in the anterior position as a slight and gradual curve, with its concavity directed to the left. This impression is seldom seen in the left oblique position but is well seen in the right oblique position, as a gentle curve, 5 or 6 cm long, with the concavity directed anteriorly. In an adult with a long and narrow thorax this curve may disappear during deep inspiration, but in a child it assumes such prominence that this finding should be judged with caution.

In mitral stenosis with slight enlargement of the left auricle a study of the impression of the left auricle in the anterior position is seldom decisive, because the chief esophageal displacement is backward, even in the right oblique position it is often difficult to say whether the curve is normal or abnormal. Some help is derived from a study of the upper segment of the curve, because abruptness of this portion is caused by the atrial prominence of the left auricle. With moderate or marked distention of the left auricle, the esophagus is seen in the anterior position to be displaced to the right and in the right oblique position to be displaced backward.

With enlargement of the left ventricle, the impression of the left auricle may be altered in a similar manner to that seen in enlargement of the left auricle. With enlargement of the left ventricle, however, the impression is seen in both oblique views, and the alteration is in the lower portion of the curve.

In aneurysm of the descending aorta the curve of the deformed left auricle is best seen in the left oblique position.

The impression of the descending aorta in the healthy subject is a gentle curve situated just above the diaphragm, with its concavity to the left in the anterior and in the left oblique position and a little to the right in the right oblique position. Its chief significance lies in the demonstration of changes in this portion of the aorta caused by syphilis and atheroma. Aneurysm displaces the esophagus forward and to the left. Atheroma, with resulting elongation of the descending aorta, may be declared by elongation, by increased depth of the impression and, of course, by increased density of the aorta.

Parkinson and Bedford¹¹ have described a translucent triangle surmounting the aortic arch, which may be seen in the roentgenogram of the chest in the left oblique position. It is proposed as a landmark, additional to the aortic window, to simplify roentgenographic measurement of the aorta and identification of certain other structures in the thorax. The right border of the aortic triangle is formed by the left subclavian artery, the left border by the spine and the base by the arch of the aorta.

This triangle is diminished by elevation, elongation or dilatation of the aortic arch, it is enlarged by conditions which lower the aortic summit and by emphysema. It is often possible to determine the diameter of the aorta by measuring the distance between the base of the aortic triangle and the upper limit of the aortic window.

11 Parkinson, J, and Bedford, D E. The Aortic Triangle. A Radiological Landmark in the Left (or II) Oblique Position, *Lancet* 2 909, 1936.

McGinn and White¹² and Kautz and Pinner¹³ have emphasized the importance of epicardial fat in roentgen studies of the heart. The chief importance lies in nonrecognition, which may lead to a considerable error in the roentgenographic measurement of the size of the heart.

ELECTROCARDIOGRAPHY

Recent interest in electrocardiography has centered around the study of chest leads. That they are valuable may be taken as an established fact, and their routine use should be encouraged.

There is still some difference of opinion regarding the optimal placing of the electrodes. Undoubtedly, more work is necessary before this question can be settled to the satisfaction of all. We see no sufficient reason yet to alter our earlier statement that for routine examination it seems wise to use a single chest lead (lead IV) with electrodes applied to the area over the cardiac apex and to the left leg. Rarely it may be necessary to apply the chest electrode in other positions over the thorax. It has been shown and reemphasized recently¹⁴ that when the chest electrode is applied just to the right of the sternum at the level of the third rib, the resulting curves are especially suitable for the interpretation of auricular components, and when the electrode is applied over the apical area of the heart, the resulting curves are especially suitable for the interpretation of ventricular components of the electrocardiogram. The so-called indifferent electrode is usually placed on the left leg when the chest lead is taken, although Wolferth and Wood have said that they feel that something may be lost unless this electrode is placed on the back.

Because the "precordial" electrocardiogram is determined largely by the variations in potential from the chest electrode, any considerable shift in location of this electrode or in the position of the heart will affect to an important degree the resulting curves. Hence criteria for the normal deflections in lead IV are defined with difficulty. The initial ventricular deflection usually consists of a sharp downward deflection (Q), 1.5 mm or more in amplitude, followed by a sharp upward deflection (R), 1.5 mm or more in amplitude. The ST segment is usually very short, beginning at or slightly below the iso-electric

12 McGinn, S., and White, P. D. Epipericardial Fat. Its Nonrecognition a Common Cause of Error in X-Ray Measurement of Heart Size, *J. A. M. A.* **107** 200 (July 18) 1936.

13 Kautz, F. G., and Pinner, M. Extrapericardial Fat Bodies, *Am. J. Roentgenol.* **35** 40, 1936.

14 Lian, C., and Golblin, V. Intérêt nosographique et pratique de la détermination précordiale auriculaire, *Ann. de méd.* **29** 721, 1936. Hecht, H. Brustwandableitungen in der klinischen Elektrokardiographie, *Deutsches Arch. f. klin. Med.* **179** 1, 1936.

level and quickly merging with T, which in adults is inverted and from 2 to 10 mm in amplitude. Absence of the Q wave or displacement of the ST segment is the most significant abnormality which may occur, alterations in the T wave are more commonly seen but are of lesser significance. It has been known for some time and reemphasized lately¹⁵ that in children the T wave is usually upright or diphasic but may be inverted as it is in normal adults.

Lead IV has shown its greatest usefulness in the diagnosis and prognosis of coronary heart disease, especially coronary occlusion.

After infarction of the anterior wall of the heart the first electrocardiographic change is usually a lowering of the ST segment in lead IV. This is followed by a marked decrease in amplitude or abolition of Q and by an upward deflection of T in the same lead. During recovery the ST segment usually reverts to the normal position, the T wave may or may not become inverted again, but the Q wave rarely reappears. Not only may the electrocardiographic alterations in lead IV be the first to declare the presence of acute infarction of the anterior wall, but they may persist, even though all other electrocardiographic evidence of infarction has disappeared. For patients with angina pectoris in whom there is no clinical evidence of previous coronary thrombosis, lead IV may give the only electrocardiographic evidence that myocardial infarction has taken place.¹⁶

After infarction of the posterior basal portion of the heart there is usually no significant alteration in lead IV. Sometimes, however, the first sign of infarction is seen in an upward displacement of the ST segment in this lead. Occasionally there are changes in the T wave, T may become deeper than normal or upright.

There is some current interest, with little publication as yet, in myocardial infarction which produces inversion of T in lead I or leads I and II, an upright T wave in lead IV and persistence of Q in lead IV. For patients showing these electrocardiographic abnormalities there is apparently a good prognosis, and as yet there is little or no information obtained at autopsy. It is probable that the infarct causing such changes is small and located laterally or marginally.

In rheumatic heart disease the T wave in lead IV may become upright. Because an upright, diphasic or polyphasic T wave in this

15 (a) Rosenblum, H, and Sampson, J. J. A Study of Lead IV of the Electrocardiogram in Children with Especial Reference to the Direction of Excursion of the T-Wave, *Am Heart J* **11** 49, 1936. (b) Rabinow, M, Katz, L. N., and Bohning, A. The Appearance of the T-Wave in Lead IV in Normal Children and in Children with Rheumatic Heart Disease, *ibid* **11** 88, 1936.

16 Levine, S. A., and Levine, H. D. An Electrocardiographic Study of Lead IV, with Special Reference to the Findings in Angina Pectoris, *Tr A Am Physicians* **1** 303, 1935.

lead is common for normal children, single tracings in individual cases add no valuable information^{15b} Serial electrocardiograms may supply suggestive data, but it cannot be emphasized too strongly that it is difficult to take serial records which are strictly comparable, for the reasons just given

Lead IV of the electrocardiogram may be abnormal in cases of pericarditis, but only rarely should these abnormalities be confused with those seen in coronary heart disease In fact, lead IV frequently may be helpful in the differential diagnosis

The electrocardiogram in acute cor pulmonale (and perhaps other instances of enlargement of the right ventricle) apparently resembles the electrocardiogram in infarction of the posterior wall of the heart, except that the T wave in lead IV is upright

Digitalis in large doses may affect lead IV, this is seen in the elevation of the ST segment and even elevation of the T wave itself

In the various other types of cardiac disease lead IV apparently is not of great value Further study, however, may require alteration of this point of view

In the understanding of the arrhythmias lead IV is not necessary The only exception to this is in regard to the chest lead which yields curves illustrating particularly auricular activity It should be emphasized that when defects in intra-ventricular conduction are present, lead IV is usually bizarre and cannot be interpreted in the usual manner

Two of the numerous other electrocardiographic studies¹⁷ will be reviewed

Heard, Burkley and Schaefer^{17a} obtained electrocardiograms from 11 human fetuses, using direct leads The fetuses were from 9½ to 25 weeks old The electrocardiographic deflections in both the limb and the chest lead resembled those of adults Normal sinus rhythm was present in all, although it was interrupted in some cases by various

17 (a) Heard, J D , Burkley, G G , and Schaefer, C R Electrocardiograms Derived from Eleven Fetuses Through the Medium of Direct Leads, *Am Heart J* **11** 41, 1936 (b) Hamburger, W W , Katz, L N , and Saphir, O Electrical Alternans A Clinical Study with a Report of Two Necropsies, *J A M A* **106** 902 (March 14) 1936 (c) Katz, L N , and Robinow, M The Appearance of the Electrocardiogram in Relation to the Position of the Heart Within the Chest, *Am J M Sc* **192** 556, 1936 (d) Tigges, F Das Elektrokardiogramm bei Hypoxämie, *Ztschr f Kreislaufforsch* **28** 225, 1936 (e) Berliner, K The Effect of Calcium Injection on the Human Heart, *Am J M Sc* **191** 117, 1936 (f) Schwartz, S P Studies on Transient Ventricular Fibrillation IV Observations on the Clinical and Graphic Manifestations Following the Revival of the Heart from Transient Ventricular Fibrillation, *ibid* **192** 808, 1936 (g) Graybiel, A , and White, P D Complete Auriculo-Ventricular Dissociation A Clinical Study of Seventy-Two Cases with a Note on a Curious Form of Auricular Arrhythmia Frequently Observed, *ibid* **192** 334, 1936 (h) Delius, L , and Opitz, E Ueber Veränderungen des Elektrokardiogramms bei Morbus Addison, *Deutsches Arch f klin Med* **178** 1, 1936

arrhythmias Slight sinus arrhythmia was present in 4 cases Comparison of the conduction time in the human adult with that in the fetus shows that in the latter to be only slightly shorter The several waves are described in detail

Hamburger, Katz and Saphin^{17b} have described 2 cases of so-called electrical alternans This disorder is extremely rare, and while it may appear in several forms, the underlying mechanism is probably identical in all instances Electrical alternation is a sign of grave prognostic significance

CONGENITAL HEART DISEASE

Aikin¹⁸ has presented 6 cases of a congenital aortic anomaly, with postmortem observations in 2 cases, consisting of total persistence of the right aortic arch, combined with persistence of the left aortic arch in the form of the left subclavian artery, an isthmus stenosis and a diverticulum of the aortic arch (left descending dorsal aortic root) The right arch was situated behind the esophagus and the left arch in front of the trachea

According to Aikin

The cases all present characteristic x-ray findings which are (1) a shadow to the right of the sternum, running upward to the head of the right clavicle, with a distinct systolic pulsation, (2) slight displacement of the trachea, and definite displacement of the esophagus to the left, (3) absence of the normal aortic knob on the left side, or only a small shadow of the descending arch on the left side, in some cases two aortic knobs, one on each side, (4) in the right oblique position the aortic knob lies behind the trachea and esophagus, both of which are displaced forward and to the left (most characteristic of all is the circular forward displacement of the esophagus by the arch of the aorta), (5) shadow of the diverticulum either in the retroesophageal knob or in the descending arch on the left side, (6) in the left oblique position a wide shadow of the ascending aorta to the right of the trachea and evidence that the aortic arch runs behind the esophagus to reach the left side

The following clinical signs were found in the six cases (1) dullness to the right of the sternum, (2) visible systolic pulsation in the second and third right intercostal spaces, (3) palpable, strong pulsation in the right supraclavicular fossa, (4) maximum intensity of the aortic sounds in the region of the head of the right clavicle, (5) slight displacement of the trachea to the left, (6) tracheal tug, (7) delay in passage of the stomach tube at the level of the third dorsal vertebra, with transmitted pulsation from the arch of the aorta

Taussig¹⁹ has presented in detail reports of 2 cases of congenital malformation of the heart due to defective development of the right

18 Aikin, A Double Aortic Arch with Total Persistence of the Right and Isthmus Stenosis of the Left Arch A New Clinical and X-Ray Picture, *Am Heart J* 11 444, 1936

19 Taussig, H B The Clinical and Pathological Findings in Congenital Malformations of the Heart Due to Defective Development of the Right Ventricle Associated with Tricuspid Atresia or Hypoplasia, *Bull Johns Hopkins Hosp* 59 435, 1936

ventricle associated with atresia or hypoplasia of the tricuspid valve. For the first time this congenital abnormality has been correctly diagnosed ante mortem, and the clinical findings described are sufficiently characteristic to determine a new clinical syndrome.

A description of this abnormality follows.

The central feature in this congenital malformation is the diminutive size of the right ventricle. The associated malformations can be postulated from the fact that the right ventricle does not function. The failure of the ventricle to function means that neither the tricuspid valve nor the pulmonary valve can function, and hence they are either atresic or markedly hypoplastic. Furthermore, it means that the only way for the blood to escape from the right auricle is through some defect in the interauricular septum. The extent of this defect determines whether the heart functions as a biloculate or triloculate heart.

Clinically, the malformation is associated with persistent cyanosis and no murmurs. The diagnosis is established through the recognition of the diminutive size of the right ventricle. This condition can be recognized in the roentgenogram by the peculiar outline of the cardiac shadow. In the A-P view, because of the absence of the pulmonary conus, the upper contour of the cardiac shadow immediately to the left of the sternum has a concave instead of a convex outline. In the left anterior oblique position the small size of the right ventricle is indicated by the absence of cardiac shadow anterior to that of the aorta. These observations are substantiated by the electrocardiogram which shows a left axis deviation.

The differentiation between a functionally biloculate and a triloculate heart depends upon the size of the interauricular septal defect. If there is free communication between the two auricles, i. e., functionally a biloculate heart, physical examination yields no additional positive findings. In contrast, when the interauricular septum is well formed, it causes obstruction to the outflow of blood from the right auricle. Under these circumstances, the auricular pulsation is transmitted to the liver and is readily palpable at its margin. It is this pulsation at the edge of the liver occurring in conjunction with a diminutive right ventricle which distinguishes a functionally triloculate from a functionally biloculate heart.

Abbott²⁰ has published an excellent monograph on congenital cardiac disorders.

RHEUMATIC HEART DISEASE

The possible relationship between the hemolytic streptococcus and rheumatic fever is still much under discussion.²¹ Undoubtedly an attack of acute rheumatism is often preceded by infection of the upper respiratory tract with the hemolytic streptococcus. After the infection of the respiratory tract there may be a symptom-free period of a few days or weeks before the rheumatic symptoms are apparent. Many

20 Abbott, M. E. *Atlas of Congenital Cardiac Disease*, New York, American Heart Association, 1936.

21 Coburn, A. F. *Observations on the Mechanism of Rheumatic Fever*, *Lancet* 2 1025, 1936.

investigators have said that they believe this sequence is the rule and consider it as partial proof of the intimate if not etiologic rôle of the hemolytic streptococcus. This is supported by a large body of immunologic evidence, which shows there is often a relationship between development and intensity of the immune response to hemolytic streptococci and the rheumatic process.

On the other hand, rheumatic fever develops in many patients who have no history of previous infection of any kind and whose serum shows no abnormal concentration of streptococcic immune bodies. Furthermore, it has been observed clinically and shown experimentally that rheumatic fever may be reactivated by events other than streptococcic infection. Without reviewing this subject further, it may be stated categorically that the evidence is insufficient to establish a causal connection between streptococcic infection and rheumatic fever.

The concept that rheumatic fever may be due to the combined influence of vitamin C deficiency and infection is finding little support either clinically or experimentally. It has, however, stimulated interest in the study of vitamin C metabolism in this disease.²² Criteria for a diagnosis of latent scurvy are being worked out, and the relation of infection and fatigue to storage and excretion of vitamin C is being investigated.

The recent investigations suggesting that a filtrable virus may play an etiologic rôle in rheumatic fever were reviewed last year in some detail. Swift²³ has pointed out that if a virus were etiologically significant in rheumatic fever but required some synergic influence for its activation, this would explain a number of features of the disease. Here again the whole truth is unknown and must await further study.

The relationship between rheumatic fever and rheumatoid arthritis has been ably discussed by Dawson and Tyson.²⁴ This problem is discussed on the basis of (1) familial relationship, (2) geographic distribution, (3) initiating factors, (4) seasonal incidence, (5) age incidence and clinical manifestations in different age periods and (6) pathologic similarities and immunologic findings. The strongest evidence that the two diseases are intimately related and possibly different manifestations of the same fundamental pathologic process is found in those numerous cases of a transitional nature in which it is impossible to decide which disease is present. Naturally, a final understanding cannot be reached until the etiology of both diseases is established.

22 Rinehart, J. F. An Outline of Studies Relating to Vitamin C Deficiency in Rheumatic Fever, *J. Lab. & Clin. Med.* **21**:597, 1936.

23 Swift, H. F. The Nature of Rheumatic Fever, *J. Lab. & Clin. Med.* **21**: 551, 1936.

24 Dawson, M. H., and Tyson, T. L. The Relationship Between Rheumatic Fever and Rheumatoid Arthritis, *J. Lab. & Clin. Med.* **21**: 575, 1936.

Gross and his co-workers²⁵ have continued their important studies on certain clinicopathologic aspects of rheumatic heart disease. New macroscopic and microscopic data on the development of the rheumatic lesions in the valves and in their rings, together with a discussion of the factors which determine the spread of infection and the localization of lesions, have been presented. In approximately 66 per cent of 60 cases of active rheumatic fever there were lesions in the bundle of His. The nature of these lesions was discussed. The gross and microscopic pericardial lesions in 87 cases of active and inactive rheumatic fever were discussed. It was possible to divide the cases into five clinical groups, and the pathologic lesions as a whole fell into three more or less characteristic histologic patterns.

Recent information regarding the evaluation of rheumatic fever has changed to an important degree the clinical conception of this illness. It is now recognized that in the acute or subacute stages many structures, in addition to the heart and joints, may show manifestations of disease.²⁶ Furthermore, it has been shown that in the early decades of life a significant degree of rheumatic heart failure is, with few exceptions, due to active disease. Consequently, signs of mild infection have been carefully sought for and studied. Most of the clinical signs have long been known but have not received the general acceptance or the proper emphasis they deserve. The practical value of certain laboratory tests, especially sedimentation tests of the blood and electrocardiography, are well established.

A symptom sometimes difficult to evaluate in children is pain in the legs. Shapiro²⁷ has attempted to differentiate between rheumatic and nonrheumatic pain on the basis of clinical observation. It was found that rheumatic children with pain in the legs usually point to the joints as the location of the maximum pain, at one time or another all the extremities are involved, the patients complain mostly during the day, especially on first arising, the pain is intensified on motion, there is difficulty in walking, and a limp is frequently noted. On the other

25 Gross, L., and Friedberg, C. K. Lesions of the Cardiac Valves in Rheumatic Fever, *Am J Path* **12** 855, 1936, Lesions of the Cardiac Valve Rings in Rheumatic Fever, *ibid* **12** 469, 1936. Gross, L., and Fried, B. M. Lesions in the Auriculoventricular Conduction System Occurring in Rheumatic Fever, *ibid* **12** 31, 1936. Friedberg, C. K., and Gross, L. Pericardial Lesions in Rheumatic Fever, *ibid* **12** 183, 1936.

26 Bourne, G. Acute Rheumatic Meningitis, *Brit M J* **2** 1017, 1936. Wolffe, J. B., and Brim, C. J. The Abdominal Syndrome of Rheumatic Disease in Childhood, *Am J Dis Child* **52** 296 (Aug.) 1936. Coburn, A. F., and Kapp, E. M. Observations on the Development of the High Blood Sedimentation Rate in Rheumatic Carditis, *J Clin Investigation* **15** 715, 1936.

27 Shapiro, M. J. The Natural History of Childhood Rheumatism in Minnesota, *J Clin & Lab Med* **21** 564, 1936.

hand, nonrheumatic children with pains in the legs locate the pain in the muscles of the leg and are unable to define any point of maximal discomfort, the upper extremities are rarely involved, the children complain chiefly after going to bed and sometimes awake crying two or three hours after going to sleep, and motion, massage and heat cause the pain to disappear

Bland, Jones and White²⁸ have studied 1,000 young patients with the physical signs of rheumatic valvular heart disease during the first ten years after the onset of rheumatic infection and have observed a regression of these signs in a considerable number and a total disappearance of all clinical evidence of cardiac disease in 83. In a few instances cardiac dilatation during the stage of acute rheumatism may have been responsible for the murmurs heard, and the decrease in the size of the heart during recovery may have been responsible for their disappearance. These authors never observed the disappearance of either a very loud diastolic murmur ending in a loud crescendo presystolic roll or a loud aortic diastolic murmur when the peripheral circulatory signs of free aortic regurgitation were present.

Regarding the treatment of active rheumatism and its manifestations, the chief interest at present is in fever therapy²⁹. This interest began a few years ago by a chance observation. A child suffering from chorea was given phenylethylhydantoin for sedation. A typical reaction developed, with a rash and fever. Surprisingly, the choreiform movements disappeared in a short time. It was soon discovered that the essential factor was the rise in temperature. Many hundreds of patients with chorea have now been treated with some form of fever therapy. According to the published results, the course of the chorea can be greatly shortened. Apparently only rarely does a patient fail to respond to this treatment, and unfavorable effects have been negligible.

Now chorea is a symptom and is associated with other symptoms of active rheumatic infection in all save a small percentage of cases. Consequently the effect of fever therapy on rheumatic carditis also was necessarily observed. Reports indicate that the presence of sub-

28 Bland, E. F., Jones, T. D., and White, P. D. Disappearance of the Physical Signs of Rheumatic Heart Disease, *J. A. M. A.* **107** 569 (Aug 22) 1936.

29 Sutton, L. P., and Dodge, K. G. Fever Therapy in Chorea and in Rheumatic Carditis With and Without Chorea, *J. Lab. & Clin. Med.* **21** 619, 1936. Neymann, C. A., Blatt, M. L., and Osborne, S. L. The Treatment of Chorea Minor by Means of Electropyrrexia, *J. A. M. A.* **107** 938 (Sept 19) 1936. Barnacle, C. H., Ewalt, J. R., and Ebaugh, F. G. Artificial Fever Treatment of Chorea. Preliminary Report, *ibid.* **106** 2046 (June 13) 1936. Weisman, D., and Leslie, C. Treatment of Sydenham's Chorea with Typhoid Paratyphoid Vaccine, *New York State J. Med.* **36** 1587, 1936.

acute rheumatism is not a contraindication to this treatment. In fact, there is suggestive evidence that the fever has a beneficial effect not only on the chorea but on the rheumatic carditis itself. Undoubtedly there will be much further investigation along this line. At present the experience with fever therapy in active rheumatism apart from chorea has been too limited to allow any conclusion to be drawn.

Marinesco and his co-workers³⁰ have made a careful clinical and anatomic study of a patient with chorée molle or "limp chorea." An abstract of the case report follows.

A girl aged 15 years began to complain of involuntary movements of the hands eleven months after an attack of acute polyarticular rheumatism. Her illness was rapidly aggravated, and within a month she could neither walk nor talk, because of involuntary movements which involved most of the skeletal muscles. This was soon followed by a paralytic state ("limp chorea") which was associated with severe toxic infection and acute endocarditis. The reflexes, which had been normal, disappeared, and the patient gradually went into coma and died. Necropsy revealed mitral endocarditis, various lesions in the central nervous system and marked degenerative changes in the muscles. It was thought that the hypotonia or paralysis was not due to lesions in the nervous system but probably to lesions in the muscles themselves.

BACTERIAL ENDOCARDITIS

Welch, Murdock and Ferguson³¹ used various methods to produce valvular lesions in rabbits with streptococci of the alpha or beta types which have the ability to show a diphtheroid-like phase on suitable mediums. Of the 35 rabbits tested 7 showed lesions on the cardiac valves which resembled grossly and microscopically, the vegetations seen in subacute bacterial endocarditis in human beings. These lesions were all on the left side of the heart, and all revealed short chains of streptococci and diphtheroid-like forms. Twelve of the 35 animals showed neither gross nor microscopic lesions on the cardiac valves, the remaining 16 showed lesions on the mitral or aortic valves that did not resemble the typical lesions of subacute bacterial endocarditis. These lesions were about 1 mm in diameter and reddish and occurred along the line of closure or nearer the bases of the valves. Microscopic study revealed a few red blood cells and a few strands of fibrin adherent to the endothelium, which was swollen and in some instances broken. There was a mild cellular reaction but suitably stained sections did not show bacteria. These nonbacterial lesions were thought to be caused by the streptococci which were injected into the rabbits and to represent the initial stage in the development of subacute bacterial endocarditis.

30 Marinesco G, Drăganescu S, Axente S, and Bruckner, I. Etude anatomo-clinique d'un cas de chorée molle. *Ann de méd.* 40 397, 1936.

31 Welch, H, Murdock, T P, and Ferguson, J A. Subacute Bacterial Endocarditis Produced in Rabbits with Streptococci That Resemble Diphtheroids. *J Lab & Clin Med* 21 1264, 1936.

Cornil, Mosinger and Jouve³² made a careful histologic study of an Osler node removed twenty-four hours after its appearance in a case of typical subacute bacterial endocarditis. They confirmed the view that these nodules are not embolic phenomena but the fusion of a series of small inflammatory lesions involving the minute vessels and the surrounding tissues.

Riesman, Kolmer and Polowe³³ reported 4 cases of subacute bacterial endocarditis in which splenectomy was performed. In each instance the operation was well borne, and the authors said they felt sure that life was prolonged and made more comfortable. It is suggested that this procedure be given consideration in the symptomatic treatment of this disease. In the discussion of this paper at the meeting of the Association of American Physicians, Lord Horder said he felt that there was no justification for such treatment.

ARTERIAL HYPERTENSION

The question of hyperepinephrinemia and hypertension has received renewed consideration. Kuré and his co-workers³⁴ found that stimulation of the splanchnic nerves in dogs always causes an increase in blood pressure and hyperepinephrinemia. These two effects usually run parallel but occasionally they are separated, that is, the rise in blood pressure may be considerable yet the hyperepinephrinemia may be slight, or vice versa. They argued that in their experiments the increase in blood pressure even with slight hyperepinephrinemia must have been related to the adrenal glands, because all other structures which might have released a pressor substance were cut out of the circulation. They attempted to explain this phenomenon on the basis of experiments by Ruzsnyák and Szent-Györgyi, who have shown that the pressor substance elaborated by the adrenal glands is not epinephrine itself but its precursor *novo*-epinephrine. This epinephrine ester has a far stronger pressor action than epinephrine. Thus, if it remains unsplit for some time, such a circumstance could explain the rise in blood pressure, with only slight hyperepinephrinemia, because epinephrine combined with lipoids probably is not detectable as epinephrine. Kuré and his associates said they believe that hyperfunction of the adrenal glands cannot be ruled out as the cause of hypertension simply because hyperepinephrinemia is not found.

32 Cornil, L., Mosinger, M., and Jouve, A. X. Contribution à l'étude histologique du nodule d'Osler, *Ann d'anat Path* **13** 675, 1936.

33 Riesman, D., Kolmer, J. A., and Polowe, D. Splenectomy in Treatment of Subacute Bacterial Endocarditis, *Am J M Sc* **192** 475, 1936.

34 Kuré, K., Okinaka, S., Ohshima, K., Shimamoto, T., and Okamura, D. Blutdrucksteigerung bei Nebennierenreizung und Hyperadrenalinämie, *Klin Wchnschr* **15** 477, 1936.

Pickering and Kissin³⁵ presented evidence against the view that essential hypertension and chronic nephritic hypertension are due to hyperepinephrinemia. They found the susceptibility of the minute facial vessels to epinephrine and their ordinarily dilated state in essential and their sometimes unconstriated state in nephritic hypertension facts which do not reconcile with the view that the raised blood pressure is due to hyperepinephrinemia. In regard to the claim that patients with chronic nephritic hypertension are abnormally sensitive to epinephrine, they found nothing in their tests to support this view.

Pickering³⁶ observed the changes in the arterial blood pressure produced in anemic subjects by transfusion of blood from patients with essential hypertension. These changes were found to be slight and no greater than those produced by transfusion of an equal value of normal blood. He said he feels that this result is opposed to the idea that the raised blood pressure in essential hypertension is due to excess of pressor or deficit of depressor substances in the circulating blood.

In considering the relationship between renal disorders and hypertension, it is of the greatest significance that permanent arterial hypertension may be produced experimentally in dogs by renal ischemia without material decrease in renal function. In experimental hypertension Wood and Cash³⁷ find that the rise in blood pressure is not proportionate to the degree of renal insufficiency and that marked hypertension does not necessarily accompany even severest insufficiency. Thus, while hypertension is in some way related to reduction or alteration of renal tissue, it is largely independent of renal function. Thus far there has been no explanation of the exact mechanism by which this hypertension results. It is probably of chemical origin, because it has been shown experimentally that the renal nerves play no part in its production. This view has received support from the clinical studies of Pickering³⁸. He has shown that not only in chronic nephritis but in essential hypertension the factor causing vasoconstriction is non-nervous. On the other hand, the temporary hypertension associated with acute nephritis is probably of nervous origin in most cases.

The controversy still goes on regarding the rôle of the pituitary gland in arterial hypertension. Marañón and Domenech,³⁹ from data

35 Pickering, G. W., and Kissin, M. The Effects of Adrenaline and of Cold on the Blood Pressure in Human Hypertension, *Clin. Sc.* **2** 201, 1936.

36 Pickering, G. W. The Effect of Introducing Blood from Patients with Essential Hypertension into Other Human Subjects, *Clin. Sc.* **2** 185, 1936.

37 Wood, J. E., and Cash, J. R. Experimental Hypertension—Observations on Sustained Elevation of Systolic and Diastolic Blood Pressure in Dogs, *J. Clin. Investigation* **15** 543, 1936.

38 Pickering, G. W. The Peripheral Resistance in Persistent Arterial Hypertension, *Clin. Sc.* **2** 209, 1936.

39 Marañón, G., and Domenech, F. Variations of Blood Pressure in Diseases of the Hypophysis, *Brit. M. J.* **2** 851, 1936.

they collected, made the categorical statement that the hypophysis has nothing to do with the regulation of blood pressure. However, they immediately went on to say that in Cushing's disease the high pressure may be explained by the concurrent hyperfunction of the adrenal glands. Jores⁴⁰ was equally emphatic in saying that overproduction of the adrenotropic hormone of the anterior lobe of the pituitary gland is the cause of the increased blood pressure in essential hypertension. This view is based on the discovery of a substance in the serum of hypertensive persons which calls forth alterations similar to those of the adrenotropic hormone of the hypophysis and which has similar chemical characteristics.

For some time the cold pressor test has been used for measuring the reactivity of the blood pressure. On the basis of this test Hines and Brown⁴¹ have divided all subjects with normal blood pressure levels into two groups: (1) those with "normal" or minimal reactions and (2) those with "abnormal" or excessive reactions. They said they believe that essential hypertension affects only those in the second group, and the transition has been observed in 3 cases. It is pointed out, however, that essential hypertension may not affect all hyperreactors. Pickering and Kissin,⁴² on the basis of a small series of observations, were unable to confirm the view that a relatively great rise of blood pressure in response to a cold stimulus is peculiar to potential or acquired essential hypertension.

In regard to the treatment of arterial hypertension, the chief interest still centers in the various operative procedures.⁴² These procedures have as their basis either the reduction of the activity of the adrenal glands or the sympathetic denervation of a large vascular area or both. The evidence that the adrenal glands play a significant rôle in arterial hypertension is inconclusive except, of course, in the case of pheochromatic tumors of the glands, the evidence that abnormal nervous vasoconstriction is a factor in causing abnormally high blood pressure is likewise inconclusive, save in rare instances. In fact, the main body

40 Jores, A. Die Bedeutung der Hypophyse für die Entstehung des Hochdruckes insbesondere der essentiellen Hypertonie, *Klin Wchnschr* **15** 841, 1936.

41 Hines, E. A., and Brown, G. E. The Cold Pressor Test for Measuring the Reactivity of the Blood Pressure. Data Concerning Five Hundred and Seventy-One Normal and Hypertensive Subjects, *Am Heart J* **11** 1, 1936.

42 (a) Heuer, G. J. The Surgical Treatment of Essential Hypertension, *Ann Surg* **104** 771, 1936. (b) Adson, A. W., Craig, W. M., and Brown, G. E. Surgery and Its Relation to Hypertension, *Surg, Gynec & Obst* **62** 314, 1936. (c) Smithwick, R. H. The Value of Sympathectomy in the Treatment of Vascular Disease, *New England J Med* **216** 141, 1936. (d) Ritch, C. O. Urologic Lesions Masked as Essential Hypertension, *Illinois M J* **70** 74, 1936. (e) Roch, M., Martin, E., and Sciclounoff, F. Les injections intraveineuses de solutions glucosées hypertoniques, leur action et leur emploi chez les brightiques hypertendus, *Ann de med* **39** 286, 1936. (f) Palmer, R. S. The Efficacy of Medical Treatment in Essential Hypertension, *New England J Med* **215** 569, 1936.

of evidence strongly suggests that in chronic nephritic and essential hypertension the high blood pressure is of nonnervous origin. As Pickering³⁸ has pointed out, although there is little doubt that vasoconstriction of nervous origin does constitute a considerable fraction of the peripheral resistance in permanent hypertension, just as it does in normal subjects, it probably does not constitute the abnormal factor responsible for the raised arterial pressure. If this is true, resection of the splanchnic nerves, for example, would lower the blood pressure simply by abolishing the normal nervous vasoconstrictor tone to a large vascular area. However, as Phemister has emphasized, the excision of normal structures, with abolition of normal physiologic processes, should not cure disease as does excision of pathologic structures. This is emphasized by the fact that the decrease in vascular tonus consequent to the destruction of sympathetic innervation is largely regained either by regeneration of the nerves or by the increased susceptibility of the denervated vessels to circulating hormones and possibly to other pressor bodies.

These considerations have been borne out fairly well in clinical practice. Heuer,^{42a} in a carefully studied group of hypertensive patients, reported that section of the anterior roots cannot be expected to cause a permanent reduction of more than 25 per cent of the preexisting systolic and diastolic blood pressures. When the initial pressure is raised not far above normal, this operation may reduce it to within the normal range, but if the initial pressure is very high, a 25 per cent reduction is less significant. Symptomatic improvement, however, is usually marked. Heuer's results with section of the anterior roots are a little better than those of Adson,^{42b} probably owing to better selection of patients, as the latter has pointed out.

Heuer's results with resection of the splanchnic nerves were disappointing, although Adson^{42b} and Smithwick^{42c} were encouraged with their results and said that it is the procedure of choice. Further observations will be necessary to evaluate the surgical treatment of permanent hypertension. In general, the results are disappointing. The fact that some patients benefit considerably indicates that a proper selection of patients might yield encouraging results.

CORONARY HEART DISEASE

Angina Pectoris—Essex and his co-workers⁴³ have described an interesting series of observations on the flow in the coronary arteries in the intact dog in response to a variety of stimuli, such as drugs, food and exercise. After a Rein thermostromuhr unit had been fixed around the circumflex artery, tests were made over periods as long as

43 Essex, H. E., Herrick, J. F., Baldes, E. J., and Mann, F. C. Blood Flow in the Circumflex Branch of the Left Coronary Artery in the Intact Dog, *Am J Physiol* **117** 271, 1936.

fourteen days Every effort was made to determine the blood flow under as nearly normal conditions as could be devised As a rule, the animal took food and water, ran about the laboratory and behaved in such a manner that a casual observer would not suspect the presence of the unit in the thorax

Determinations of the blood flow were made on the quietly resting dog, and in a number of instances daily values were obtained that fell within the experimental error of the method (10 per cent) Epinephrine caused a transient augmentation in flow from two to four times the control values, the augmentation did not last longer than seven minutes in any of the tests, and, as a rule, the major effect terminated three minutes after the injection, thus paralleling the known effect of doses of epinephrine on the blood pressure of the dog

Repeated observations indicated that glyceryl trinitrate in intravenous doses of 0.22 mg resulted in a temporary increase in coronary blood flow, which at its maximum was about twice the control value However, the increase was of short duration, since it usually was over four or five minutes after the injection Within two minutes after the inhalation of amyl nitrite the coronary flow increased to about twice the control value Although the animal continued to breathe the drug, the blood flow did not remain at twice the control level for more than two minutes, when it declined to a value from 20 to 30 per cent above the control In one experiment a second ampule was administered six minutes after the effect of the first ampule had been dissipated Only a slight elevation in coronary blood flow followed, which clearly indicated that the dog is refractory to a second dose given too soon after the first dose

In response to appropriate doses of thyroxin, increases of coronary flow as great as 244 per cent above the control values were observed from forty-eight to ninety-six hours after the injection was given An increase of coronary flow of as much as 84 per cent was observed during the digestion of food

The effect of exercise on coronary blood flow was especially interesting When the exercise was begun there was an immediate rise in coronary flow, which attained maximal values in about five minutes, after which it gradually subsided to a much lower level in the succeeding five minutes The flow remained relatively steady at the lower level until the amount of exercise was increased, whereupon the flow again rapidly increased for about five minutes, after which it declined to a lower level, but remained above the second level reached during the previous increment in exercise When exercise was stopped the flow rapidly fell to or below the values for controls

The results of these studies are in general accord with those previously reported but have especial importance because of the less abnormal experimental conditions

Mainzer and Josephthal⁴⁴ have undertaken a comprehensive consideration of the rules governing the 'localization and radiation of pain in angina pectoris. They began with some well known facts, they pointed out that anginal pain is characteristically located behind the sternum or in the precordial region, that the pain commonly radiates to the left and less commonly to the right, that the radiating pain may appear a little before the discomfort in the cardiac area, that in general the attacks are similar in a given person but dissimilar in various patients and that the radiation is frequently dependent on the strength of the attack, a weak attack causing slight substernal pain, a stronger attack causing substernal pain with radiation to the left arm and a still stronger attack causing substernal pain with radiation to both arms.

These remarkable characteristics of the radiation have been discussed by Daniélopolu. He showed, on embryologic grounds, that the left side of the heart is supplied chiefly by left-sided nerves and the right side of the heart by right-sided nerves. Hence, in ischemia of the left side of the heart any radiation of the pain should be to the left, and the greater frequency of left-sided radiation coincides with the greater incidence of left-sided coronary sclerosis. Daniélopolu said he considers that an anginal attack which in the beginning calls out radiation of pain to the left and later, with increasing intensity, also to the right, may be explained by a jumping over of the stimulus from the left to the right side in the spinal cord. Other investigators have suggested different possibilities, and each has supported his view with clinical observations.

Fundamental to Mainzer and Josephthal's investigations are the facts that the larger part of the left ventricle, especially in its entire anterior wall, is supplied with blood by the left coronary artery, whereas the right coronary artery supplies the greater part of the right ventricle and a portion of the posterior wall of the left ventricle. Therefore, if the seat of muscular injury is important in determining the radiation of anginal pain, it would be expected that circulatory disturbances involving the left coronary artery would be associated with radiation of pain to the left, while circulatory disturbances involving the right coronary artery would be associated with radiation of pain to the right.

A carefully selected group of patients with angina pectoris were studied and classified as having pain with a central localization or with right-sided or left-sided radiation or both, and the electrocardiograms were classified as revealing an injury in the anterior or in the posterior wall or of indefinite localization. To the authors' 39 cases were added reports of 38 more by authors who made similarly careful observations.

⁴⁴ Mainzer, F, and Josephthal, F. Ueber die Lokalisation und Ausstrahlung des Angina pectoris-Schmerzes, *Acta med Scandinav* 89 329, 1936.

The accompanying table gives the combined figures. The results are obviously discordant and require explanation. The thought that the localizing possibilities of the electrocardiogram were overvalued is inadmissible. That this is not the case is shown by the general agreement with the observations of Buchner, Weber and Haager, whose studies were anatomically controlled. Mainzer and Josephthal said they feel that the true explanation lies in the consideration of the differences between coronary insufficiency of the right and of the left ventricles. In most patients with angina pectoris there is significant hypertrophy of the left ventricle due to previous or present arterial hypertension. Now the discrepancy between the maximal coronary flow to a normal muscle mass and a pathologically increased muscle mass is a decrease in flow to the latter, the maximal diameter of the coronary vessels is set once and for all. With the development of coronary arteriosclerosis, the relative functional insufficiency of the left ventricle becomes marked indeed. This is true to such a degree that even in predominant disease of the right coronary artery it is the overworked and hypertrophied left ventricle which comes to harm through the functional inter-

Left Sided Pain					Central Pain				Right Sided Pain				Right Sided and Left Sided Pain			
Total	Anterior Wall	Posterior Wall	Anterior and Posterior Wall (Indefinite)	Normal	Total	Anterior Wall	Posterior Wall	Anterior and Posterior Wall (Indefinite)	Total	Anterior Wall	Posterior Wall	Anterior and Posterior Wall (Indefinite)	Total	Anterior Wall	Posterior Wall	Anterior and Posterior Wall (Indefinite)
37	11	13	11	2	30	17	4	9	6	2	3	1	4	1	1	2

dependence of both circulatory territories. This explanation is in full agreement with the anatomic findings, not only in all cases of arteriosclerosis of the left coronary artery and of the narrowing of the mouths of both coronary arteries by syphilis but also in all cases of anatomic stenosis of the right coronary artery, the myocardial lesions lie in the region of the left ventricle. In those anginal attacks in which the progressive radiation of the pain depends on the strength of the attack, it is explained that with increasing intensity of the attacks the ischemic area extends to a location which will provoke the particular radiation observed.

There is little new to discuss concerning the treatment of angina pectoris⁴⁵. Of the various operative procedures, injection of alcohol

45 Beck, C. S. Further Data on Establishment of a New Blood Supply to the Heart by Operation, *J Thoracic Surg* 5 604, 1936. Kerr, H. H. Results of Superior Cervical Sympathectomy in Angina Pectoris, *South Surgeon* 5 365, 1936. Feinberg, S. C. Treatment of Coronary Artery Disease by Intravenous Injections of Hypertonic Saline Solution, *Am J M Sc* 191 410, 1936. Barach, A. L., Richards, D. W., and Parsons, W. B. Oxygen Treatment and Thyroid Ablation in Treatment of Heart Disease, *Ann Int Med* 9 1453, 1936.

into the communicating ram of the upper dorsal sympathetic nerves continues to be the most satisfactory

Coronary Thrombosis—Wiggers and Green⁴⁶ have experimentally investigated the effectiveness of drugs on collateral flow after experimental coronary occlusion in dogs. They have pointed out the many difficulties attending this problem. Observations of changes in color or comparison of size of infarcts without and with the use of a drug are subject to too many contingencies to have certain value. Testing the effects of drugs on coronary outflow or inflow does not test the response of collateral vessels, and it ignores the hemodynamic alterations resulting from occlusion of the main branch.

Attempts were made to establish a reliable criterion for determining changes in collateral coronary flow. Measuring blood flow from the distal end of a cut coronary artery was deemed too hazardous a method, both because the blood need not have passed through the infarcted area and because of the difficulty in registering the minute changes in flow. During the early phases of their work these authors saw no reason for questioning the view generally held that the pressure in the peripheral end of a cut coronary vessel represents the pressure transmitted through various collaterals and that it constitutes the pressure head for collateral coronary flow. However, it was shown in another study that this peripheral coronary pressure is due not to transmission of waves of arterial pressure but to the compressing action of the ventricle on intramural vessels and therefore does not serve as an index of collateral coronary flow.

The supposition was then considered that changes in the rate of coronary inflow of a perfused artery of the intact heart can be used as a criterion not only of changes in the flow through its distributing intramural branches but of changes in collateral supply as well. It was believed at first that changes in vascular resistance induced by drugs could probably be referred solely to vascular changes, because the ischemic region studied was not contracting. Other studies showed, however, that peripheral coronary resistance is increased just about as much when the area is stretched by the force of intraventricular tension as when tension develops through its own contraction. Thus, while this method is unsuitable as a criterion for determining alterations of collateral flow alone to an ischemic area following the use of drugs, it does offer a criterion of the changes in resistance to flow which are

⁴⁶ Wiggers, C. J., and Green, H. D. The Ineffectiveness of Drugs upon Collateral Flow After Experimental Coronary Occlusion in Dogs, *Am Heart J* 11: 527, 1936.

the result of vasomotor and extravascular effects which inescapably operate together. Since the conditions resemble those following coronary occlusion in man, this method is of considerable practical importance.

It was found that drugs of the theobromine and theophylline group and alcohol, which cause insignificant changes in mean arterial pressure, have a negligible effect on flow through an ischemic region. The nitrite group, which causes a fall in mean arterial pressure, produces a slight decrease in coronary resistance within the ischemic area. This is probably due to decrease in extra-arterial compression of coronary vessels following lowered arterial pressure, with decrease in the stretch of the ischemic area, rather than to dilatation of the vessels in this area. In any event, this slightly beneficial effect is more than offset by the lowering of pressure in other branches from which collateral flow could be derived. Pressor drugs, such as epinephrine, increase resistance to inflow in the ischemic area, if these drugs exert a dilating vascular action, it is overpowered by a greater extravascular pressure in the intact heart. The effect of 5 to 10 per cent carbon dioxide with oxygen was negligible, but in three experiments partial asphyxiation caused a slight decrease in minute flow each time.

The problem of collateral flow was attacked from yet another standpoint. It was shown previously, by means of myographs, that the muscular area supplied by the ramus descendens ceases to contract and vigorously expands within about one minute after occlusion of this artery. Now if a drug acts to increase significantly the collateral blood supply, its injection from one to two minutes after occlusion should cause some amelioration of the systolic muscular expansion and perhaps some sign of contractile recovery, such as promptly follows unclamping of the main artery. The results obtained show that the abolition of contraction after occlusion of the ramus descendens is not modified in the least by inhalation of oxygen, carbon dioxide or amyl nitrite or by therapeutic intravenous doses of various theophylline preparations, nitrites, adenylic acid or epinephrine.

The general conclusion is reached that under the experimental conditions described the collateral blood supply to an ischemic area cannot be significantly improved by the use of any drug. We feel that these experiments extend considerably the knowledge of rational treatment of acute cardiac infarction. Certainly clinical observations in most cases are in agreement. Whether these results are equally applicable to instances of sudden occlusion of small coronary arteries or to the gradual occlusion of larger ones requires further consideration. For example, the partial or complete relief of pain in some

instances of cardiac infarction following the use of vasodilating drugs has been held generally to indicate a favorable effect. This might be accomplished either by increasing the coronary flow in the infarcted area or by decreasing the work of the heart, but in either event the result would be beneficial.

Meanwhile, clinical experience continues to show the value of vasodilating drugs for occasional patients who suffer from paroxysmal angina pectoris. The mechanism by which this salutary effect occurs and the type of patient who is likely to respond favorably have not been made clear.

There have been a large number of clinical reports concerning various aspects of coronary thrombosis, of which only a few can be listed here.⁴⁷ An excellent monograph on diseases of the coronary arteries has been published under the editorship of Levy.⁴⁸

MISCELLANEOUS CARDIAC DISORDERS

Amyloidosis—There have recently been reported a number of cases of myocardial amyloidosis.⁴⁹ The heart may be affected as part of a widespread process, or it may be the chief organ involved. Only rarely is the cardiac involvement sufficient to produce congestive failure. The diagnosis is extremely difficult during life, especially in the idiopathic variety, which is not associated with preceding or concurrent chronic disease.

Nonbacterial Thrombotic Endocarditis—Gross and Friedberg⁵⁰ have described in detail the clinical and pathologic features in 47 cases of nonbacterial thrombotic endocarditis. They have classified their cases

47 Edeiken, J, and Wolferth, C C. Persistent Pain in the Shoulder Region Following Myocardial Infarction, *Am J M Sc* **191** 201, 1936. Shookhoff, C, Douglas, A H, and Rabinowitz, M A. The Sedimentation Time in Acute Cardiac Infarction, *Ann Int Med* **9** 1101, 1936. Goodrich, B E, and Smith, F J. Nonfilament Leukocyte Count After Coronary Artery Occlusion, *Am Heart J* **11** 581, 1936. Blumer, G. Pericarditis Epistenocardica, *J A M A* **107** 178 (July 18) 1936. Raab, A P, and Rabinowitz, M A. Glycosuria and Hyperglycemia in Coronary Thrombosis, *ibid* **106** 1705 (May 16) 1936.

48 Levy, R L. Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1936.

49 Kerwin, A J. Idiopathic Amyloid Disease of the Heart, *J Lab & Clin Med* **22** 255, 1936. Ferris, H W. Amyloidosis of Lungs and Heart, *Am J Path* **12** 701, 1936. Perla, D, and Gross, H. Atypical Amyloid Disease, *ibid* **11** 93, 1935. Reimann, H A, Koucky, R F, and Eklund, C M. Primary Amyloidosis Limited to Tissue of Mesodermal Origin, *ibid* **11** 977, 1935.

50 Gross, L, and Friedberg, C K. Nonbacterial Thrombotic Endocarditis: Classification and General Description, *Arch Int Med* **58** 620 (Oct) 1936. Friedberg, C K, and Gross, L. Nonbacterial Thrombotic Endocarditis Associated with Acute Thrombocytopenic Purpura, *ibid* **58** 641 (Oct) 1936.

into five groups and have presented the distinguishing features of each. This disorder is viewed by them as an accidental occurrence in the course of any fatal disease and as without appreciable significance. Its development is usually dependent on previous rheumatic damage to the cardiac valves, but occasionally it may be dependent on some toxic agent which appears to have a special predilection for endothelial structures.

Pellagra—Feil⁵¹ has stated that acute pellagra is frequently associated with cardiovascular symptoms, including dyspnea, palpitation, tachycardia, feeble heart sounds and slight edema in some instances. The electrocardiogram was abnormal in 19 of the 38 cases studied, and in only 4 of the 19 was there any complication which might have been a factor in causing the electrocardiographic alterations. Although manifestations of cardiac disorder in pellagra are common, they are not as a rule severe.

Typhus Fever—Heizog and Rodriguez⁵² systematically investigated the pathologic changes in the heart in 103 cases of typhus fever during the last epidemic in Chile. Whereas macroscopically, save in a few instances, there were no detectable changes save dilatation of the left ventricle and flabbiness of the cardiac muscle, microscopically, 97 per cent of the patients showed specific, disseminated, mostly focal interstitial myocarditis. These lesions were carefully studied and described. A special investigation of the conduction system revealed little abnormality, and this was borne out by electrocardiographic studies. The authors did not include a clinical description of the patients, but they stated that the severity of the heart failure paralleled the pathologic picture.

Carbon Monoxide Poisoning—Kroetz⁵³ has emphasized the cardiac signs and symptoms of carbon monoxide poisoning. These cardiac symptoms have been little noted, partly because of the prominence of other symptoms and partly because rescue workers are rarely trained observers.

Palpitation is the most remarkable circulatory symptom and is found without exception after this type of poisoning. According to Lewin, in the terrific explosion at Llengherydd, Wales, which resulted in the death of 440 miners, many of the rescue crew had such marked

51 Feil, H. A Clinical Study of the Electrocardiogram and of the Phases of Cardiac Systole in Pellagra, *Am Heart J* **11** 173, 1936.

52 Herzog, E., and Rodriguez, H. Die Beteiligung des Myocards beim Fleckfieber (Myocarditis exanthematica), *Beitr z path Anat u z allg Path* **96**:431, 1936.

53 Kroetz, C. Herzscheidigungen nach Kohlenoxydvergiftungen, *Deutsche med Wchnschr* **62** 1365, 1936.

palpitation that it was heard by their comrades and mistaken for the knocking of the entombed miners

Disturbances of rhythm frequently, but not always, accompany the palpitation. The heart rates of previously healthy persons are found to be between 100 and 140 a minute, and this tachycardia is followed in a few days by bradycardia, often associated with high grade auriculo-ventricular block

Pain of an anginal character, with typical radiation, may appear if the inhalation of gas does not lead to unconsciousness. This is often masked by other complaints, including cough, suffocation and pain in the region of the diaphragm and in the back. In some instances actual pain may be absent, but there may be a feeling of injury in the heart. Klotz has pointed out that anginal pain may be present without the typical picture of carbon monoxide poisoning, which may be lacking because of the accompanying severe circulatory shock. There may be toxic myocarditis, which is declared by cardiac dilatation, by lowering of the blood pressure and by alteration in the heart sounds, rate and rhythm

The electrocardiographic alterations, which were long thought to be exceptional, are regular, reliable and differentially valuable signs. These alterations are more significant and usually outlast the clinical cardiac symptoms. They include abnormalities of the P wave, prolongation of the auriculoventricular conduction time, intraventricular block and alterations in the ST segment and T wave suggesting coronary disease

The Athletic Heart—Kirch⁵⁴ has added to his previous detailed studies concerning the possibility of real hypertrophy of the heart consequent to prolonged athletic training. He has said that he feels that this problem cannot be satisfactorily determined by clinical investigation only but that it must be correlated with painstaking anatomic observations. The material chiefly consisted of the hearts of 9 athletes who died suddenly between the ages of 15 and 25. They had all been healthy previously and without cardiac complaints. Painstaking anatomic studies were made, including weighing the cardiac chambers separately, measuring these chambers in various ways and relating the findings to body weight and to skeletal musculature

It is impossible here to do more than summarize briefly Kirch's conclusions. Three of the nine hearts showed definite hypertrophy. The author would reserve the term athlete's heart for such an anomaly only. The athletic heart is not a diseased heart, the hypertrophy must be considered solely as a process of adjustment, which will be reversed

⁵⁴ Kirch, E. Herzkraftigung und echte Herzhypertrophie durch Sport, Ztschr f Kreislaufforsch 28 893, 1936

as soon as the athletic activity is decreased or stopped. Whether this hypertrophy follows dilatation, as is so often true in the usual instances of cardiac hypertrophy, the author was unable to decide, he was never able to associate cardiac weakness and myocardial dilatation with the athletic heart. Often the term athletic heart is applied improperly in instances of cardiac dilatation, which is more truly an expression of cardiac weakness. Three of the nine hearts were normal, and the remaining three were slightly enlarged, occupying an intermediate place between normal size and frank hypertrophy. The author used the term *gekraftigten Herzen* (strengthened hearts) to separate them from unmistakably hypertrophied (athletic) hearts.

Neurocirculatory Asthenia—Johnson⁵⁵ became interested in a group of patients many of whom had complaints suggesting neurocirculatory asthenia and found the chloride level of the blood abnormally low. These patients were symptomatically relieved within four or five days by increasing the intake of sodium chloride. It may well be that a small percentage of patients now wrongly classified as neurasthenic may in reality be suffering from the effects of abnormally low chloride values.

CARDIAC ARRHYTHMIAS

Orgain, Wolff and White⁵⁶ have reviewed the pertinent literature and reported their studies of a series of 54 patients with auricular fibrillation and auricular flutter and without other signs of cardiac disease. Forty-seven of the 54 patients had auricular fibrillation alone, 5 had auricular flutter alone and 2 had both. The ages of the 49 patients with auricular fibrillation ranged from 21 to 75 years. The arrhythmia was paroxysmal in all but 3 cases. Definite etiologic factors were few, but many of the attacks were intimately associated with such precipitating factors as infection, alcohol, ether, burns, colic in the gall-bladder, vomiting, surgical operation, exertion and emotion. Follow-up studies of 90 per cent of the entire group revealed that the prognosis for life and for the maintenance of adequate cardiac function is good. Reassurance, the avoidance of precipitating factors and the use of quinidine sulfate were regarded as the most useful therapeutic measures.

The ages of the 7 patients with auricular flutter varied from 27 to 66 years. All the attacks were paroxysmal, the duration varying from a few minutes to five years. The common symptoms were palpitation,

⁵⁵ Johnson, A. S. Sodium Chloride Therapy, *New England J. Med.* **215** 438, 1936.

⁵⁶ Orgain, E. S., Wolff, L., and White, P. D. Uncomplicated Auricular Fibrillation and Auricular Flutter. Frequent Occurrence and Good Prognosis in Patients Without Other Evidence of Cardiac Disease, *Arch. Int. Med.* **57** 493 (March) 1936.

choking, dyspnea, dizziness, weakness and, occasionally, precordial pain. The precipitating factors were exertion, surgical operation and infection. Quinidine or quinine was used in 5 cases, being effective in restoring normal rhythm or preventing paroxysms in 3, but later proving ineffective in 1 of these. Digitalis restored normal rhythm in 1 of 5 cases in which it was tried. Quinidine, after treatment with digitalis, converted the rhythm to normal in 2 instances.

Campbell and Gordon⁵⁷ have reported on the use of quinidine in a series of 135 cases of auricular fibrillation. This drug restored normal rhythm in about two-thirds (64 per cent) and was effective in maintaining normal rhythm in about one-third (34 per cent).

It is emphasized that restoring normal rhythm and, even more so, maintaining it for a long period depend on the careful selection of suitable patients. In general, the most suitable patients are those without congestive failure or marked valvular disease, with no more than slight cardiac enlargement, in whom fibrillation has been established for less than one month.

Thorough treatment with digitalis is important before treatment with quinidine is started. Any complicating infection may prevent success. In 7 of the 135 cases embolism developed after treatment, and in only 1 instance was there a fatality which was probably due to quinidine.

Starr⁵⁸ reported on the use of acetylbetamethylcholine in the treatment of seventy-five attacks of paroxysmal tachycardia in 37 patients. He outlined the method as follows. The patient is asked to lie down. Alternate pressure over the carotid sinuses is attempted, and if this is unsuccessful in stopping the arrhythmia, acetylbetamethylcholine is given subcutaneously. If the attack does not stop promptly after the appearance of the flush, the site of the injection is vigorously massaged. If tachycardia persists, the carotid sinuses are alternately compressed while the action of the drug is undiminished. If this is unsuccessful, larger doses of the drug may be given.

Dosage varies with weight and age. For children, 10 mg may be sufficient to stop an attack, while for elderly obese persons as much as 60 mg may be necessary, an average dose is 30 mg. It is important to massage the site of the injection if a given dose is ineffective or even to increase the dose. By mistake as much as 300 mg has been given intravenously and 300 mg subcutaneously without fatal results. In instances of toxicity, atropine should be given. An antagonism exists

⁵⁷ Campbell, M., and Gordon, F. W. The Quinidine Treatment of Auricular Fibrillation, *Quart J Med* **5** 205, 1936.

⁵⁸ Starr, I. Acetyl- β -methylcholine. IV Further Studies of Its Action in Paroxysmal Tachycardia and in Certain Other Disturbances of Cardiac Rhythm, *Am J M Sc* **191** 210, 1936.

between the cardiac effects of acetylbetamethylcholine and quinidine, and these drugs should not be given together, the same is true, but in a lesser degree, in regard to digitalis

Acetylbetamethylcholine is not very effective in the treatment of auricular flutter or ventricular extrasystoles, and no permanent effect follows its use in auricular fibrillation

Gravier and his co-workers⁵⁹ were able to cure a patient with troublesome sino-auricular tachycardia by excision of the right stellate ganglion

An abstract of the case report follows

This patient was a woman aged 37 years whose heart rate was habitually moderate and was not increased unduly by effort, food or emotion. In the course of the menstrual period, however, the heart rate increased to 140 to 180 per minute and was accompanied with distressing symptoms, preventing her from leading a normal existence. Not only was medicinal therapy ineffective, but it seemed to increase the tachycardia, and as a last resort the right stellate ganglion was removed. This procedure effected a complete cure.

The authors have discussed the nature of the abnormal cardiac mechanism in this case and the rationale of treatment.

HEART FAILURE AND ITS TREATMENT

Peters and Visscher⁶⁰ have investigated the energetics of the heart in the heart-lung preparation under various conditions. They emphasize that the most important characteristic of any machine during work is its efficiency. The heart is a machine for transforming chemical potential energy into work in transporting blood around the circulatory system. The amount of energy it must expend in order to perform a given amount of work is of profound importance in the physiology, and especially in the pathological physiology, of the heart.

Their results indicated that the failing heart suffers first simply from a decrease in mechanical efficiency. The energy liberated at a given external diastolic volume remains the same, only the proportion which can be put to useful work falls off. Heart failure consists, in essence, of an alteration of the energy-utilizing and not the energy-liberating mechanism, the heart is able to liberate energy, but it is unable to put it to useful work. The authors stated the belief that the correction of this defect should be the physiologic objective in the treatment of myocardial failure.

Various substances were tested in regard to their ability to alter the capacity of the heart for work. It was shown that at constant external diastolic volume, both calcium and glucosides of the digitalis

59 Gravier, L., Tourniaire, A., and Gonnet, J. Nevrose tachycardique traitée par stellectomie droite, *Lyon med* **158** 425, 1936

60 Peters, H. C., and Visscher, M. B. The Energy Metabolism of the Heart in Failure and the Influence of Drugs upon It, *Am Heart J* **11** 273, 1936

series increase the consumption of oxygen and the efficiency of the cardiac muscle. Several reputed cardiac tonics have no direct beneficial action on the heart, for example, coramine (pyridine betacarboxylic acid diethylamine in a 25 per cent solution) produces, instead, dilatation with decreased output and efficiency.

Thompson and White⁶¹ have concluded from a review of 2,000 postmortem examinations that the commonest cause of hypertrophy of the right ventricle is strain and failure of the left ventricle. In 704 of the 2,000 cases there was hypertrophy of the right ventricle to the extent that the wall measured 5 mm or more in thickness. Of these 704 cases, clinical study revealed factors producing primary strain of the right ventricle in 64, primary strain of the left ventricle in 326, primary strain of both ventricles in 141 and no clear cause of strain in 141. Thus, in nearly half the cases the only cause of hypertrophy of the right ventricle was strain and hypertrophy of the left ventricle. Right-sided hypertrophy was often found in cases of pure left-sided strain, regardless of the presence or absence of clear clinical evidence of failure of the left ventricle, but the presence of failure increased the degree of hypertrophy. It was found that the degree of hypertrophy of the right ventricle was almost as great in cases of pure left-sided strain as it was when there had been primary right-sided strain.

Parker and Weiss⁶² have described the changes in the blood vessels and alveolar walls in the lungs in cases in which there was an advanced degree of rigid mitral stenosis associated with extreme failure of the pulmonary circulation. Their description of these changes follows:

The lesions in the pulmonary vessels consisted of (a) intimal thickening of the arteries, and (b) hyperplastic arteriolar sclerosis and arteriolar necrosis. The changes in the alveolar wall consisted of (a) marked dilatation of the capillaries, (b) increase in the thickness of the capillary basement membrane, (c) increase in the interstitial tissue (collagen), (d) interstitial pericapillary edema, and (e) a tendency of the flat epithelial cells to become cuboidal in shape.

With progressive pulmonary engorgement, first the visible capillaries increase in number, and only later do they dilate. Often the capillaries become displaced and are separated from the alveolar surface by a considerable degree of edema or by thick layers of collagen.

Permanent structural alterations in the lungs caused by circulatory failure interfere with the gaseous exchange, partly through altered permeability of the alveolar wall, and partly as a result of the simultaneous passage through the individual capillaries of numerous columns of red cells, instead of a single red cell.

61 Thompson, W. P., and White, P. D. The Commonest Cause of Hypertrophy of the Right Ventricle—Left Ventricular Strain and Failure, *Am Heart J* **12** 641, 1936.

62 Parker, F., Jr., and Weiss, S. The Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis, *Am J Path* **12** 573, 1936.

In the causation of the pulmonary arterial and arteriolar lesions, an important role is played by the prolonged combined presence of (a) high intravascular pressure, (b) stagnation of blood, and (c) edema

Coelho and Ribeiro⁶³ observed acute pulmonary edema in man, which, in the order of frequency, is caused by failure of the left ventricle, mitral stenosis, toxic states and cerebral disturbances. They said they recognize that there are additional causes which have been noted by other authors. They found that the mechanism of pulmonary edema produced in dogs by the injection of silver nitrate in the right ventricle or saphenous vein is different from the edema produced by injury to the left ventricle or complete obstruction of the aorta. In the former instances the edema is of toxic origin and identical with toxic edema in man, in the latter instances the edema is of mechanical origin and is identical with pulmonary edema produced in man by insufficiency of the left ventricle.

Smirk⁶⁴ has ably discussed certain factors which favor the development of edema in congestive heart failure.

Many observers have shown that the albumin and globulin percentages of the plasma are substantially lower in most cases of congestive heart failure, and, in general, the lesser the percentages the greater the edema. Furthermore, it has been shown that improvement in congestive failure is accompanied with a return of the colloid osmotic pressure toward normal. Smirk's observations showed that the average degree of difference in the colloid osmotic pressure of the plasma for groups of normal patients and of patients with heart failure is in the region of 6 to 10 cm. of water.

The colloid osmotic pressure of samples of edema fluid removed from patients with congestive heart failure is ordinarily between 2 and 6 cm. of water. Thus the low colloid osmotic pressure of the plasma and the presence of a colloid osmotic pressure in the edema fluid both reduce the effective osmotic pressure of the plasma. The reduction may be only a few centimeters or as great as 18 cm. of water. It is a well known fact that, apart from congestive heart failure, one may have a fall in the osmotic pressure of the plasma of 10 or 15 cm. of water below the normal without the development of edema, and one may deduce that the fall in the effective osmotic pressure in congestive heart failure is usually insufficient of itself to insure the development of edema.

63 Coelho, E., and Ribeiro, M. Etude expérimentale sur deux formes pathologiques de l'œdème du poumon mécanique et toxique, *Arch. d. mal. du cœur* 29 383, 1936.

64 Smirk, F. H. Observations on the Causes of Oedema in Congestive Heart Failure, *Chn. Sc.* 2 317, 1936.

Smilk next considered whether the capillaries in congestive heart failure and in health are equally permeable to water with its dissolved crystalloids. This was studied by comparing the rates of passage of fluid out from blood vessels under equal filtration pressures. The results indicated that if the average transudation rate is called 100 per cent in the normal, it is 200 per cent in the experiments in which a correction is applied for the low colloid osmotic pressure of the plasma and 260 per cent in the experiments in which no such correction is made.

The relationship between venous pressure and edema also was studied. Smilk mentioned some of the variables to be considered in relating an increase in the venous pressure to the formation of edema. Although a straight line relationship has been shown between the degree of artificial venous congestion in normal human subjects at rest and the rate of formation of edema, it is felt that this should be regarded as a remarkable coincidence rather than strong evidence that edema fluid is a simple filtrate of plasma and that a balance of the forces of the capillary pressure and of the osmotic pressure of the plasma is largely responsible for the interchange of fluid through the capillary blood vessels.

In resting patients with congestive heart failure the venous pressure in the legs is a few centimeters less than the general venous pressure plus the pressure of a vertical column of water extending from the manubrium to the place where the venous pressure is measured, the same is true for normal subjects. Active muscular movements of the legs diminish this pressure by from 10 to 100 cm of water. Thus the incapacity for exercise of patients with congestive heart failure increases the average venous pressure in the legs throughout the day to much above normal. In congestive heart failure the general venous pressure, measured in relation to the manubrium, seldom exceeds 10 cm of water. At rest a rise of 10 cm in general venous pressure will produce a rise of about 10 cm in the veins of the leg, but the average rise of pressure throughout the capillary bed is less than the rise of venous pressure which causes it. Many good arguments are given to show that a uniform rise of 10 cm of water in capillary pressure, apart from its secondary effects on blood vessels, is insufficient in itself to cause edema. However, such an increase in filtration pressure will naturally increase the transudation of fluid from blood vessels.

It is clear that in many cases of congestive heart failure several factors acting in varying degree contribute toward the development of edema, their importance in regard to treatment is obvious.

Kalter ⁶⁵ has used amino-acetic acid in degenerative heart disease and congestive heart failure. The theoretical basis for the use of amino-acetic acid in cardiac disease is made clear, and an analogy is drawn with its use in progressive muscular dystrophy. Cases are cited in which amino-acetic acid was apparently of considerable benefit in the treatment of cardiac failure. We have used this drug in a few cases of heart failure, with definite benefit in 2 instances.

⁶⁵ Kalter, S. Ueber Glykokollbehandlung degenerativedystrophischer Herzmuskelerkrankungen, *Deutsche med. Wchnschr.* **62** 1371, 1936.

Book Reviews

Parenteral Therapy A Ready Reference Manual of Extra-Oral Medication By Walton Forest Dutton, M D, and George Burt Lake, M D Cloth Price, \$7 50 Pp 386, with 90 illustrations Springfield, Ill Charles C Thomas, Publisher, 1936

It is the usual task of the reviewer to set before his readers the reasons for buying or reading any new work that is brought to his attention. If there are no such reasons, the work is, as a general rule, ignored. Occasionally, it becomes the reviewer's unpleasant duty to point out the general worthlessness of a book and even its potential dangers.

The book under present consideration is divided into three sections. The first deals with the general technic of parenteral therapy. It includes descriptions of the methods of giving or attempting to give medicaments by all the parenteral routes now in use. It discusses blood transfusion, intracardiac injections, pneumothorax and paracentesis of all the serous spaces. It describes surgical procedure such as the administration of an anesthetic, the treatment of injection of material into the veins and the injection treatment of hernia.

This part of the work is well done. The authors make no claim to originality. They have merely collected data on the well known methods. One wonders why it should have been done at all. Surely, a textbook is not needed to describe the technic of hypodermic and simple intravenous medication. These methods need no encouragement, they are overdone now. The more complicated methods are in the nature of major surgical procedures and should not be attempted by any one without an adequate period of training. Thyroidectomy or cholecystectomy should not be attempted with no further training than a perusal of a description of the technic. Neither should cisternal puncture or ventricular puncture or even blood transfusion be performed. There is even less excuse for the publication of the second and third parts of the book. The second part is a therapeutic index. Here are listed diseases and under each the drugs (parenteral) that may be used to advantage. One learns that alopecia may be treated with salts of arsenic, antuitrin, pilocarpine or glycerophosphates. Asexualism yields to testicular, ovarian and pluriglandular preparations or viriligen. A journey to the lower end of the alphabetic list informs one that goiter vaccine (Houda) is recommended in both thyroid deficiency and thyrotoxicosis. And so on, ad nauseam.

The third portion consists of pharmacologic notes. This is an alphabetic arrangement of a large number of drugs all of which lend themselves to parenteral administration. Most of these drugs are listed under their trade names, and the manufacturer is not neglected. It is impossible to mention all the ridiculous compounds that have found their way into this collection. Adrempco is a solution representing the entire pituitary, thyroid and adrenal glands and the ovaries and testicles. The list of gold preparations reminds one of Thompson's work entitled "The Quacks of Old London." Again one meets goiter vaccine (Houda) and viriligen, and one finds the remarkable statement that strychnine is marketed by Merck & Co, Inc, and others.

The authors state in the preface that they have not had personal experience with all the drugs listed in the index and naively remark that they have studied the statements of the manufacturers but assume no responsibility for the results that may follow the use of any of these remedies. This does not constitute a valid excuse. Since the publication and discussion of a remedy implies tacit approval unless the reverse is stated, it seems that these authors have assumed a weighty responsibility.

Considerable time has been spent by the reviewer in saying what might have been said in a few words, namely, this book should never have been released.

Die Nebennierenrinde By Sigismund Thaddea, M.D. Price, 11 marks
Pp 199, with 78 illustrations and 36 tables Leipzig Georg Thieme, 1936

The author of this monograph is an assistant in the Second Medical University Clinic of the Charite Hospital in Berlin. He has painstakingly assembled the material for a review of the development of knowledge concerning the adrenal cortex from the original description of the adrenal glands by Eustachius in 1563 down to the present time. He is to be congratulated on the success of his work. The author has arranged his material according to a well planned sequence. He begins with a historic account of the adrenal glands, next he discusses the morphology and function of the adrenal cortex and then he describes the isolation of the cortical hormone and animal experiments to prove the many effects of this hormone. Finally, he devotes a section of the book to the clinical aspects of Addison's disease and other conditions in which the function of the adrenal cortex is deficient and to the treatment of these conditions that may be logically employed. A bibliography of 640 well chosen references, arranged in alphabetic order and covering the literature of the entire world, is included.

A monograph of this character, well put together and well printed and accompanied with clear illustrations, cannot fail to be serviceable. It will be of use largely for reference purposes to medical students and teachers and therefore should soon be available in any good library to which students have access.

Le diabète sucré Questions controversées de clinique et de pathogénie
By E. Aubertin, E. Bessière, P. Broustet, O. Hirsch, P. Mauriac, R. Saric,
M. Traissac and F. J. Traissac Price, 32 francs Pp 214 Paris Masson
& Cie, 1936

This book consists of a series of lectures by various physicians at the hospital Saint-Andre de Bordeaux on different aspects of diabetes, such as nervous complications, ocular complications and intermittent diabetes. The material is of some interest but is not new for the most part.

La syphilis gastrique By Anastase Landau and Joseph Held Price, 32 francs
Pp 185 Paris Masson & Cie, 1936

Landau and Held thoroughly present the subject of gastric syphilis in this monograph. They include not only organic gastric disease but functional gastric disturbances due to extragastric syphilis. The monograph includes a discussion of the incidence, pathology, classification and treatment of the disease, the disturbances in the secretory function of the stomach as a result of syphilis and the difficulties encountered in making a differential diagnosis of gastric syphilis. It includes also a good bibliography, mostly of French and German works and many x-ray plates.

Nothing particularly new is added to the subject, however, the monograph is a good clinical discussion of gastric syphilis.

Theory and Practice of Psychiatry By William Sadler Price, \$10 Pp
1231 St. Louis C. V. Mosby Company, 1936

Dr. Sadler gives an excellent and comprehensive discussion of his subject without going to extremes. He rides no special hobby, shows no signs of psychiatric "cultism" and evolves no new philosophy. On running through this excellent compendium, the reviewer (who is not a professional psychiatrist) is impressed anew, however, with the difficulties of the whole subject. The psychiatrist of the modern school tends to state in technical and often incomprehensible terms what is fairly obvious to any one dealing with patients, one is consumed by the heat but obtains little light. A feeling becomes uppermost that perhaps methods of case finding and classification have outrun useful therapy. After all, the constitutional basis must be paramount in most of the unhappy persons who drift into the psychiatrist's net, and, while the writer does not minimize this fact, he dismisses it in a relatively brief section.

MONOCYTIC LEUKEMIA

REPORT OF SIX CASES AND REVIEW OF ONE HUNDRED AND
TWENTY-SEVEN CASES

EDWIN E OSGOOD, M D

PORTLAND, ORE

Since 1913, when the first case of monocytic leukemia was reported by Reschad and Schilling-Torgau, more than one hundred cases have been described. The majority of these reports have appeared since the publication of the excellent reviews of Dameshek and Clough. It is the purpose in this paper to summarize the essential data from the literature, to report 6 more cases and to discuss the origin of the monocyte as deduced from a study of blood smears in 32 cases¹ and of the sternal marrow in 4 of these.

REPORT OF CASES

CASE 1—A S, a school girl 7 years of age, was first seen on Jan 30, 1934, complaining of swelling of the jaw and an itching rash. She was well until January 17, when a painless swelling of the gums and left submaxillary region and an itching rash were noted. A dentist was consulted, and he found no cause for the swelling of the gums. The patient had been exposed to scabies in school. Dr Ray W Oldenburg, of Klamath Falls, Ore, was consulted on January 21. He found generalized enlargement of the lymph nodes and a leukocyte cell count of 5,000, with some cells which were difficult to classify. From the blood smear sent to me a tentative diagnosis of monocytic leukemia was made. Dr Oldenburg² referred the patient to me, and I first saw her on January 30. Petechiae were noted on the legs on January 23, and the swelling of the gums and submaxillary nodes had increased. Hemorrhage from the gums occurred on January 29. The child felt well except for itching of the skin.

The significant physical findings were marked swelling of the gums, a small infected area covered by a whitish membrane opposite the lower left first molar, cutaneous lesions, generalized lymphadenopathy and splenomegaly. The cutaneous lesions were of two types, one group being typical of scabies and the other constituting a petechial rash over the upper portion of the chest. The submaxillary,

From the Department of Medicine, the University of Oregon Medical School

1 These 32 smears included those from the 6 cases here reported, 22 demonstrated by Dr Roy R Kracke in the scientific exhibit of the American Medical Association at Milwaukee in 1933, 1 sent to me by Dr A G Foord, of Pasadena, Calif, and 3 given to me by Dr Frank Heck, of the Mayo Clinic

2 Dr Oldenburg has given me permission to report this case

cervical, axillary, epitrochlear and inguinal nodes showed two or three plus enlargement, and the left submaxillary node showed four plus enlargement. All the enlarged nodes were discrete, firm, painless and freely movable. Kramer's dullness and D'Espine's sign were present, indicating enlargement of the posterosuperior mediastinal nodes. The spleen was just at the costal margin and was somewhat firm and not tender. The enlargement of the mediastinal nodes was confirmed by fluoroscopy and a roentgenogram of the chest. The results of the studies of the blood are shown in table 1. The white cell count varied from 1,000 to 7,300, with from 1 to 7 per cent monocytes, from 1 to 20 per cent promonocytes and from 24 to 9 per cent monoblasts. The sternal marrow obtained on January 31 consisted almost entirely of monoblasts, with a few promonocytes (fig 1). The monocytes, promonocytes and monoblasts showed a negative peroxidase reaction. A diagnosis of acute subleukemic monocytic leukemia and scabies was made.

TABLE 1—*Hematologic Studies*

Case	Date	Hemo- globin, Gm per 100 Cc	Red Blood Cells, Millions per Cu Mm	White Blood Cells per Cu Mm	Monocytes, Percentage	Promono- cytes, Percentage	Mono- blasts, Percentage
1	1/31/34	11.22	4.07	5,050	1.6		24
	2/ 2/34	10.91	4.01	5,450	7.0		
	2/ 3/34	11.59	4.02	3,250	6.0		
	2/ 5/34	10.29	4.11	3,750	6.0	1.0	
	2/ 6/34	10.55	3.89	5,750	7.0		
	2/ 7/34	9.70	3.28	5,050	7.0	2.0	4.0
	2/ 8/34	8.82	3.72	7,300			5.0
	2/ 9/34	9.00	3.53	5,500	2.0	1.0	6.0
	2/10/34	10.48	3.56	4,450	1.0	15.0	9.0
	2/12/34	11.73	3.99	2,450		20.0	5.0
	2/13/34	11.59	4.07	2,750	2.0	16.0	6.0
	2/14/34	9.29	3.18	1,000		8.9	3.5
2		6.21	2.00	3,450			
		5.24	1.78	4,425	60.0		
	2/ 6/35	4.14	2.00	8,250	48.0		
	2/ 9/35				42.0	34.0	13.0
	2/ 9/35*						73.0
	2/15/36			20,350			
3	2/21/35	7.65	2.40	54,000			
	2/23/35	6.69	1.92	38,650	60.0	1.0	1.0
4	8/16/35*				5.0	26.5	1.5
	8/24/35	8.56	2.94	27,100	44.0		
5		10.21	3.64	151,000		65.0	4.0
6	4/21/36	11.04	3.36	21,300	40.0		
	4/29/36	8.56	2.65	25,750	29.0		
	5/ 1/36			34,450	15.0	8.0	5.0
	5/ 5/36	8.97	3.14	22,950	32.0	7.0	Occasional

* Sternal marrow was studied

The patient was admitted to the Doernbecher Memorial Hospital for Children on February 2. The scabies responded quickly to treatment. Sodium perborate paste was applied to the gums after every meal, and a mouth wash of hydrogen peroxide was used every half hour while the patient was awake, in an attempt to prevent Vincent's stomatitis, which occurs as a rule in these cases. Three roentgenographic treatments of about one twentieth of an erythema dose were given over the gums and the anterior portion of the chest on February 2, 7 and 12, and two treatments were given to the spleen, spine and dorsal portion of the thorax. Two transfusions of 250 cc each were given on February 9 and 11. Infection of the gums was controlled, and the enlargement of the nodes decreased slightly. No discomfort was noted by the patient until February 15, when nausea and vomiting developed. She then complained of a generalized aching pain over the body, especially in the lumbar region, which was controlled by codeine. The tempera-

ture was above normal for the first time on February 4 and rose steadily, reaching 106.6 F on the evening of February 14. The gums became swollen to such an extent that they extended well above the surface of the teeth. They were entirely free from infection. The patient died at 12:20 a. m. on February 16.

Necropsy—Gross examination showed petechiae and ecchymoses in the skin. The gums were so swollen that they hid the teeth from view, yet there was no ulceration or bleeding. Generalized enlargement of the lymph nodes and spleen (120 Gm.), multiple hemorrhages in the various serous membranes and hyperplasia of the bone marrow in both the flat and the long bones were noted.

Microscopic examination revealed leukemic infiltration of the lymph nodes, spleen, lungs and liver and surrounding infarcts in both kidneys. Such infiltration was evident also in the appendix, in Peyer's patches of the ileum, in the marrow of both flat and long bones and in the gums. The leukemic infiltrations consisted of monocytes, promonocytes and monoblasts, with a few plasma cells. Many of the promonocytes showed phagocytosed red blood corpuscles. The epithelium of the gums was intact and showed no indications of either necrosis or

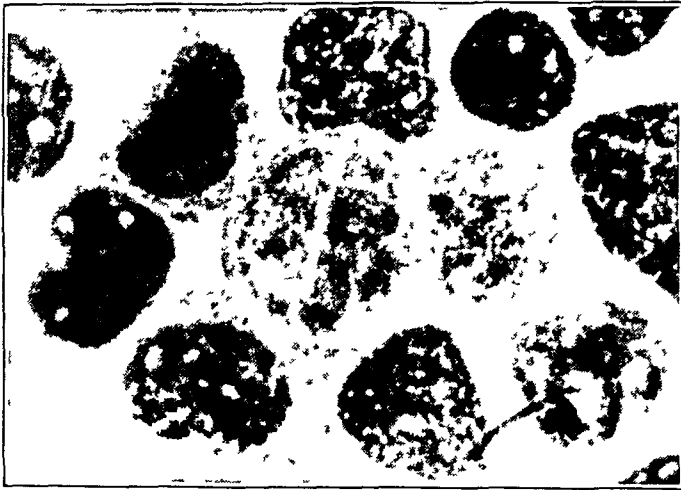


Fig 1 (case 1)—Photomicrograph ($\times 1,200$) of sternal marrow. One monocyte, two promonocytes and three monoblasts are shown.

infection, the swelling being entirely due to the leukemic infiltration. No transition between lymphocytes and monocytes was observed in the lymph nodes. In both the spleen and the lymph nodes the monocytes had almost crowded out the other types of cells. In the liver the infiltration was confined, as in lymphatic leukemia, to the region of the portal trinites. The marrow from the rib and the middle third of the tibia showed almost complete replacement by monoblasts and highly phagocytic promonocytes. Reticulum cells in the marrow and spleen showed no evidence of hyperplasia.

CASE 2—A woman 36 years of age consulted Dr C. E. Watts,³ of Seattle, on Feb. 1, 1935, complaining of a cutaneous rash and nosebleed. She had not felt well since August 1934 and had noticed a cutaneous rash, which had been diagnosed by a dermatologist as erythema multiforme. She had also received treatment for endocervicitis. Physical examination revealed an unusual maculopapular eruption on the face, neck, hands and feet, including the palms and soles,

³ Dr Watts supplied the report of the history and physical examination and gave me permission to report this case.

and petechiae on the thighs (fig 2) She had a profuse nosebleed The submaxillary and axillary nodes showed one plus enlargement The spleen was not palpable but was enlarged to percussion The white cell count was 3,450, with many immature cells The red cell count was 2,000,000, with a normal color index.

On the basis of a blood smear sent to me for examination, a tentative diagnosis of acute monocytic leukemia was made Examination of sternal marrow, obtained on February 15 and sent to me by Dr Watts, showed a nucleated cell count of 170,000 per cubic millimeter, with nearly all the cells monoblasts or promonocytes, thus confirming the diagnosis of monocytic leukemia The patient had a temperature of 100 to 101 F, and swelling and ulceration of the pillars of the



Fig 2 (case 2) —The cutaneous lesions in monocytic leukemia

fauces developed, but there was only slight swelling of the gums The cervical lymph nodes became considerably enlarged The data for the blood are given in table 1 Death occurred on February 17

Necropsy, by Dr A Balle, of Seattle, revealed multiple hemorrhages in the skin, lungs, heart, liver and spleen, with leukemic infiltration of these organs, with generalized enlargement of the lymph nodes, with the liver extending 5 cm below the costal margin and with the spleen approximately three times the normal size A bicornuate uterus and double vagina were noted The pathologist stated that because many of the cells showed a positive reaction for peroxidase he felt that this was a case of acute myelogenous leukemia, but the blood smears and preparations of the sternal marrow which I examined showed clearly that the immature cells belonged to the monocyte series

CASE 3—R L, a man aged 62, entered the Multnomah County Hospital on Feb 20, 1935, complaining of "boils." He had been well until the spring of 1933, when the first boil developed on the chest. Since that time he had had numerous boils scattered over the body. At the time of his admission to the hospital there was a large carbuncle on the back of his neck. Since December 1934 he had noticed frequent epistaxis and increased weakness. The lesion on the back of the neck began to develop on Feb 1, 1935.

Physical examination showed that the temperature ranged from 96 to 100 F and that the pulse rate ranged from 72 to 112. The respiratory rate was 20, and the blood pressure was 100 systolic and 70 diastolic. There was a large carbuncle on the back of the neck. No swelling of the gums, petechiae or enlargement of the lymph nodes was noted. The spleen and liver were slightly enlarged to percussion. The white cell count varied from 38,650 to 54,000, with 60 per cent mature monocytes. The hemoglobin value ranged from 6.69 to 7.65 Gm, and the red cell count ranged from 1,920,000 to 2,940,000. The details of the studies of the blood are shown in table 1. A diagnosis of chronic monocytic leukemia with myelophthisic anemia and carbuncle of the neck was made. The patient died on February 28.

Necropsy revealed, in addition to the carbuncle and furunculosis, enlargement of the spleen (425 Gm) and liver (2,250 Gm), petechiae in the pericardium and leukemic infiltration, consisting chiefly of mature monocytes in the kidneys, spleen, lymph nodes and marrow. The infiltration in the liver was chiefly in the periportal areas. There was terminal bronchopneumonia.

CASE 4—H R. R., an Italian aged 64 years, entered St Vincent's Hospital on July 30, 1935, under the care of Dr Roy C McDaniels⁴. He complained of loss of weight and fatigue. He had been well until January 1934, when he noticed general malaise, with increasing fatigability and loss of weight. The total loss of weight was 35 pounds (16 Kg).

Physical examination revealed generalized pallor of the skin and mucous membranes and a two plus enlargement of the spleen, but no petechiae, no swelling of the gums and no enlargement of the lymph nodes or liver. The white cell count was 27,100, with 44 per cent monocytes. The sternal marrow on August 16 showed 5 per cent monocytes, 24 per cent promonocytes, 2.5 per cent promonocytes in mitosis and 1.5 per cent monoblasts.

A diagnosis of monocytic leukemia was made by Dr T D Robertson, pathologist for St Vincent's Hospital, and I confirmed this diagnosis when I saw the patient in consultation. Details of the studies of the blood are shown in table 1. The patient was discharged from the hospital on August 29, feeling somewhat improved. After that he felt better and gained some weight, but a year later he was emaciated, weak and anemic, and, according to Dr Robertson, so many monocytes and promonocytes were present in the blood that there was no question as to the correctness of the diagnosis. He died about March 13, 1937.

CASE 5—Mrs J D, a woman aged 76, was first seen on Oct 18, 1935, by Dr Laurence Selling,⁵ of Portland, Ore. She complained of weakness and a "cold" and showed nothing significant on physical examination except hyperemia of the pharynx. On October 23 the temperature was 99.2 F, and redness of the pharynx was still present. The patient was seen daily thereafter by Dr Selling.

4 Drs Roy C McDaniels and Thomas D Robertson, of Portland, Ore, gave me permission to include a report of this case. A full report will be given by them in a separate paper.

5 Dr Selling gave me permission to report this case.

TABLE 2—Summary of Cases of Monocytic Leukemia

Case	Authors	Number	Age	Sex	Swollen Gums	Petechiae	Enlarged Lymph Nodes	Enlarged Spleen	Enlarged Liver	White Blood Cells	Monocytes, %	Promonocytes, %	Monoblasts, %	Peroxidase Reaction	Duration of Illness	Necropsy	Comment
1	Reschad and Schilling		33	M	+	+	0	+	+	15,100	56,000	72.0	74.0	—	9 wk	+	Cutaneous lesions
2	Torgau		47	M	+	+	—	+	+	3,700	36,000	25.0	65.0	?	75 mo	+	Biopsy of sternal marrow followed typhus
3	Fleischmann		48	M	+	+	—	+	+	4,500	16,500	44.0	—	?	9 wk	+	
4	Bingel	1	5	M	—	+	+	+	+	21,000	—	87.0	0.2?	—	5 wk	—	Not described
5	Rosenthal, 1921	2															
6		3	34	M	0	0	0	+	+	660	3,000	44.0	—	?	4 mo	+	
7	Komlya and Hayashi		20	M	+	+	+	310	1,250	52,800	317,500	30.0	80.0	+	5 wk	+	Probably acute myelogenous leukemia
8	Lwald, Frehse and Hennig	1	32	M	+	+	0	0	0	140,000	—	80.0	87.0	?	21 days	+	Probably acute myelogenous leukemia, lymphocytes
9		2	30	M	0	0	0	0	0	99,600	—	5.0	7.0	+	6 wk	+	Probably acute myelogenous leukemia
10		3	29	F	0	0	0	0	0	56,000	—	00.0	—	?	?	+	Probably acute myelogenous leukemia
11	Fwald		60	M	+	0	0	+	—	15,000	—	0.2	—	+	6 wk	+	Probable case
12	Alder	7	30	M	+	0	0	0	0	100,000	—	40.5?	—	?	Few wk	?	Probable case
13		8	78	M	0	0	0	0	0	8,000	46,000	36.5?	—	?	3 mo	?	Probable case
14		12	57	F	+	0	—	—	—	80,000	400,000	70.0?	—	?	14 days	?	Probable case
15	Naegeli	2	34	M	+	+	+	—	0	7,800	126,000	13.27.5	10.2	?	25 mo	+	
16	Hoff	4	41	M	+	0	0	390	0	1,800	2,500	15.0	42.5	—	75 wk?	+	
17	Merklen and Wolf		30	M	—	+	0	+	0	20,500	43,000	85.0	93.0	?	3 mo	+	Probably acute lymphatic leukemia
18	Swirszczewskaja	27		M	—	—	—	+	+	6,400	416,000	1.6	3.1	—	85 mo	+	
19	Meierovitch		19	M	+	0	+	+	+	11,000	80,000	75.0	59.0	?	?	+	Questionable case
20	Ugrumow	30		M	0	+	+	+	+	36,000	—	46.5	—	?	23 days	+	
21	Hannema	11		M	+	+	+	+	+	107,000	120,000	81.0	—	?	19 days	+	
22	Hittmair, 1928	63		M	+	0	+	+	+	33,200	—	83.0	—	+	1 mo	+	
23	Tschistowitsch and Bykowa	63		M	0	0	+	500	1,650	6,000	6,600	1.0	7.5	?	15 mo	+	Acute aleukemic type
24	Weissenbach, Martha neu, Raulot La Pointe, Bourdillon and Ronget	52		M	—	+	+	+	0	13,200	198,000	34.0	73.0	?	14 mo	—	Cutaneous lesions, tuberculous
25	Wyschegorodzewa	38		F	+	—	—	310	1,610	1,900	22,700	16.0	83.0	—	8 mo	+	Cutaneous lesions, pains in bones, sternal puncture
26	Sega and Brustolon	18		M	+	+	+	263	2,160	34,740	40,780	55.4	—	?	2 mo	+	Cutaneous lesions
27	Muenzel	8		M	+	+	+	+	—	8,000	52,000	3.0	82.0	?	3 wk	—	
28	Farley	62		F	+	+	—	0	0	10,000	72,000	46.0	95.0	+	10 mo	—	
29	Dias	6		F	0	0	0	0	0	3,730	4,030	48.0	55.0	?	3 mo	—	Questionable case
30	Bock and Wiede	34		M	—	+	+	870	0	10,000	46,000	54.0	85.0	?	22 days	+	Sternal marrow normal
31	Rosenthal, 1930	4	0	0	0	0	0	0	0	73,000	146,000	70.0	78.0	?	?	?	

32	Dameshek	1	55	M	+	—	+	+	+	19,300	147,000	20 5 75 5	+	3 mo	—	Cutaneous lesions, pains in bones Biopsy of sternal marrow
33	Hittmair, 1930	2	70	M	+	—	—	—	—	13,300	124,000	19 0 86 8	—	10 wk	—	
34	Clough	62	0	F	+	+	+	+	+	160,000	28 6 55 0	0 5	—	14 days?	+	
35	Castellano and Girar	45	62	M	+	+	+	+	+	174,000	262,000	87 0	—	?	+	
36	det		45	F	0	+	—	—	—	79,800	93,400	18 0 39 0	?	?	—	
37	Lawrence, Josey and Young	1	0	M	+	+	+	+	+	9,300	47,500	42 0 86 5	+	3 mo	—	
38		2	61	F	0	0	+	+	+	8,100-20,000		30 0 51 5	+	?	0	Biopsy of sternal marrow, remission after radiation
39	Cooke	3	13	M	+	+	+	+	+	18,800	180,700	66 0 83 0	+	4 wk	+	
40	Schwarz	19	30	M	+	—	+	+	+	50,000	87 0		—	4 wk	—	
41	Chutrecasas and Ur	0	0	M	0	+	+	+	+	13,000	104,000	46 0 89 0	+	5 wk	—	Pains in bones
42	tubey									287,000	366,000	95 0 99 0	?	13 mo	—	
43	Rucks and Cunnig	60	60	F	0	+	—	—	—	5,000-36,000		13 0 51 0	?	6 mo	+	Monoblasts included pro monocytes
44	Invernizzi	27	27	M	+	+	+	+	+	70,000		85 0	?	5 6 wk	—	Joint pains, large hematoma, cerebral hemorrhage
45	Asselstine	1	35	M	+	+	+	+	+	198,000	380,000	5 0 82 0	?	4 mo	+	
46	Bohne and Hulsmans	2	33	M	+	+	+	+	+	7,400	12,000	0 0 64 0	?	?	+	
47	Reich	50	50	F	—	—	—	—	—	1,800	4,200	3 0 27 0	—	25 yr	+	
48	Gardner	33	33	M	+	+	+	+	+	8,100	52,300	14 0 69 0	?	9 wk	—	
49	Fontana	47	47	F	+	+	+	+	+	17,800	246,600	6 0 80 0	?	51 days	+	Biopsy of marrow, probably myelogenous leukemia
50		43	43	M	—	—	—	—	—	1,400	250,000	66 0	?	4 yr 5 mo	?	
51	Sydenstricker and Phinzy	47	47	F	+	+	+	+	+	3,500	168,000	47 0 89 0	—	4 mo	—	
52	Farrar and Cameron	55	55	M	+	+	+	+	+	11,400-210,000		0 0 80 0	+	7 mo	—	
53	Pellegrini	68	68	M	0	—	—	—	—	38,000	105,000	80 0	?	3 5 mo	?	Blateral exophthalmos
54	Mesropyan	2	40	M	0	0	—	—	—	44,900	93,400	64 5 80 0	?	?	—	
55	Orr	1	40	M	0	0	+	+	+	1,800	10,000	18 0 75 0	+	18 mo?	+	
56		2	71	M	0	0	+	+	+	4,400	140,000	56 0 94 0	+	3 mo	+	
57	Dubinskaja and Ba-	53	53	F	+	+	+	+	+	19,000	89,000	61 0 73 0	—	8 mo	+	Pains in bones
58	kaltshuk									28,700	42,500	79 0 89 0	?	8 wk	?	Necrotic angina
59	Andreoli and Fourest	8	8	M	0	+	+	+	+	318,000	384,000	4 0 5 0	?	10 days?	—	Cutaneous lesions
60	Olis	77	77	M	+	+	+	+	+	40,000	65,000	81 0	?	23 days	+	
61	Lucherni	1	64	M	+	—	—	—	—	40,500-285,000		13 0 48 0	?	3 mo?	+	
62	Fowler	2	43	M	+	—	—	—	—	49,000	118,000	72 0 84 0	—	5 5 mo	+	Cutaneous lesions
63		3	44	M	+	—	—	—	—	10,250	40,000	23 0 88 0	+	9 wk	—	
64	Bykowa	1	24	M	+	+	+	+	+	5,600	10,000	78 0 83 0	+	6 wk	+	Cutaneous lesions, abdominal pain with diarrhea
65																Biopsy
66	Grenet, Levent and Isaac Georges	2	24	M	0	0	+	+	+	4,600		84 0	?	9 wk	+	
67		1	3	F	0	+	+	+	+	70,000	137,400	6 0	?	?	—	
68		2	10	M	+	+	+	+	+	2,200	65,300	3 0 33 0	?	3 mo	—	
69	Tridswell	3	2 1/2	M	0	+	+	+	+	20,700-22,800		10 5 46 0	?	?	—	
		12	12	M	—	0	+	+	+	1,000	10,000	42 0	?	4 mo	+	

TABLE 2—Summary of Cases of Monocytic Leukemia—Continued

Case	Authors	Number	Age	Sex	Swollen Gums	Petechiae	Enlarged Lymph Nodes	Enlarged Spleen	Enlarged Liver	White Blood Cells	Monocytes, %	Promonocytes, %	Monoblasts, %	Reaction for Peroxidase	Duration of Illness	Necropsy	Comment
70	Feord, Parsons and Butt	1	17	M	+	+	+	+	2,400	25,100	60,000	63.0	91.0	—	7 wk	+	
71		2	22	F	+	—	+	550	2,100	1,600	37,450	1.0	94.0	—	3 mo	+	Biopsy of lymph node
72		3	58	F	+	—	+	—	0	35,400	76,000	61.0	72.0	?	11 wk	—	
73		1	52	F	+	—	+	—	—	92,700	116,800	85.0	88.0	?	15 wk	—	
74	Marchal, Barletton and Mahoudeau	1	41 to 60	M	0	0	+	+	—	1 cases				?	?	?	Two cases of persistent
75		2	60	M	0	0	+	+		80,000	334,000			?	?	?	diarrhea
76		3		M	0	0	+	+						?	?	?	
77		4		M	0	0	+	+		4 cases				?	?	?	
78		5		M	0	0	+	+		6,000	27,000			?	?	?	
79		6		F	0	0	+	+						?	?	?	
80		7		F	0	0	+	+						?	?	?	
81		8		F	0	0	+	+						?	?	?	
82	Levy	13	13	F	0	+	+	+	0	40,000	86,000	16.0	63.0	?	3 mo	?	Boils
83	Gittins and Hawksley	11 mo	11 mo	F	+	+	+	+	250	6,000	24,500	7.0	20.0	+	12 wk	+	Ovarian tumors
84	Osgood and Lyght	18	18	M	+	+	+	+	0	3,900	15,500	15.0	81.0?	+	1 mo	+	Probably not monocytic leukemia
85	Marchal, Souhé and Mahoudeau	50	50	F	0	—	+	+	0	3,200	20,000	1.0	60.0	?	1 yr	—	Pains in bones, biopsy
86	Luzina	0	0	M	0	+	+	+	+	9,200	35,000	38.5	75.5	?	3.5 mo	—	Cutaneous lesions, cerebral hemorrhage
87	Weissenbach, Bourdillon, Martineau and David	20	20	M	0	+	+	0	—	60,000	80,000	89.0	98.0	?	3 mo	—	
88	Neves and Roberto	34	34	F	+	+	+	+	—	5,500	51,300	2.0	4.0	?	24 days		Cerebral hemorrhage, hematuria
89	Chaves	1	31	M	+	+	+	+	+	34,000	180,000	88.0	96.0	+	18 mo	+	
90	Forner	2	38	M	+	+	+	+	+	19,500	364,000	71.0	95.0	—	6 wk	+	
91		3	40	M	+	+	+	+	+	72,000	242,000	85.0	98.0	+	11 wk	+	
92		4	26	M	+	+	+	+	+	52,700	73,500	77.0	81.0	+	2 wk	+	
93		5	16	F	+	+	+	+	+	74,200	160,000	67.0	94.0	+	5.5 mo	—	
94		6	32	F	+	+	+	+	+	71,000	110,000	65.0	88.0	?	3 mo	+	Biopsy
95	Foot and Oleott	234	234	M	+	0	0	310	1,130	3,900	9,000	0.0	4.0	?	14 mo	—	Boils
96	Labbe, Boulh and Balmus	29	29	M	+	0	0	—	—	28,000	30,800	54.5	59.0	?	2 mo	—	
97		67	67	M	0	0	+	+	+	6,400	23,000	18.0	24.0	?	7 mo	—	Biopsy

98	Gregg	58	M	+	—	+	625	2,050	2,650	13,200	100 80 0	100 80 0	?	?	+	Bolls, arthritis
99	Levine	65	F	+	0	—	1,000	2,250	8,500	39,000	12 0 34 0	12 0 34 0	7 mo	+	+	
100		69	F	—	0	—	150	1,500	3,000	120,000	16 0 38 0	16 0 38 0	7 mo	+	+	
101		54	M	+	0	—	500	2,500	14,500	30,400	38 0 58 0	38 0 58 0	2 mo	+	+	Chinese
102		4	M	+	+	—	190	1,300	7,200	46,450	50 0	50 0	6 wk	+	+	
103		41	M	—	+	—	950	2,250	84,800	113,200	66 0	66 0	2 wk	+	+	Negro
104		46	F	+	+	—	260	1,900	461,000	70 0	70 0	3 wk	+	+	+	
105		37	F	—	+	—	—	—	1,000	84,000	43 0	43 0	1 mo	—	—	Sternal puncture
106		8	F	—	—	—	+	+	7,400	21,600	79 0	79 0	3.5 mo	—	—	
107		23	F	—	—	—	+	+	8,000	90,000	19 0	19 0	3.5 mo	—	—	
108	Doan and Wiseman	1	M	+	—	—	260	—	1,500	130,000	36 0 80 0	36 0 80 0	1 yr	+	+	Cutaneous nodules
109		66	M	—	—	—	+	+	1,500	130,000	1 5 95 0?	1 5 95 0?	5 mo	+	+	
110		2	M	—	—	—	+	+	1,200	200,000	14 0 98 0?	14 0 98 0?	6 mo	?	?	
111		0	F	0	0	0	0	0	42,000	110,000	70 0 88 0?	70 0 88 0?	6 wk	—	—	
112		34	F	+	+	+	+	—	7,200	50,000	49 0 98 0?	49 0 98 0?	3.5 mo	+	+	Chinese
113	Morgan and Hsu	5	M	+	+	+	+	0	21,200	338,000	97 0 99 0	97 0 99 0	3.5 wk	+	+	Biopsy
114	Marchal, Brun and Grupper	30	M	0	0	+	+	+	15,600	35,400	50 80 0	50 80 0	4 mo	+	+	
115	Penati and Levi	1	F	+	+	+	390	1,400	3,700	70,900	80 77 0	80 77 0	7 mo	+	+	Sternal puncture
116		42	M	+	0	+	—	—	1,700	8,200	1 6 5 6	1 6 5 6	2 mo	—	—	Sternal puncture, necrotic angina
117	Giffin and Watkins	1	M	0	0	—	1,050	+	2,000	8,200	1 5 26 0	1 5 26 0	?	—	—	Still living, splenectomy
118		50	M	0	0	—	800	+	2,000	4,600	2 5 22 0	2 5 22 0	?	+	+	
119	Marchal, Lemoine and Bloch Michel	73	M	0	0	+	300	+	10,500	65,600	52 0 92 0	52 0 92 0	?	+	+	
120	Whitby and Christie	14	F	+	+	+	—	+	3,400	320,000	5 0 73 0	5 0 73 0	+	+	+	Rectal tumor producing intestinal obstruction
121	Haining, Kimball and Jones	34	F	—	0	0	+	0	—	0	75 0 90 0	75 0 90 0	?	+	+	Cutaneous nodules, biopsy
122	Mercer	39	M	+	0	+	+	0	21,500	40,000	41 0 54 0	41 0 54 0	?	—	—	Lesions of skin and tongue, biopsy
123		17	F	—	—	—	+	—	42,300	210,000	83 0 97 0	83 0 97 0	+	+	+	
124	Sadat	45	M	+	+	+	+	+	2,780	11,750	37 0 34 0	37 0 34 0	—	+	+	Cutaneous nodules, one or two lymph nodes enlarged
125	Mann	57	M	+	0	—	250	1,400	90,000	125,000	69 0 81 0	69 0 81 0	?	+	+	
126	Tsundomi	48	M	0	0	0	0	0	—	11,500	63 0	63 0	7 wk	+	+	Sternal puncture
127	Hawksley	10	M	—	—	—	—	—	10,000	20,000	73 0	73 0	21 mo	+	+	Sternal puncture
128	Osgood	7	F	+	+	+	120	930	1,000	7,300	1 0 7 0	1 0 7 0	30 days	+	+	Sternal puncture, cutaneous lesions
129		36	F	—	+	+	+	+	3,450	52,700	17 0 94 0	17 0 94 0	6.5 mo?	+	+	
130		62	M	—	—	—	423	2,250	38,000	54,000	60 0	60 0	2 yr?	+	+	Bolls
131		64	M	—	—	—	+	+	27,100	27,100	5 0 44 0	5 0 44 0	2 1/2 yr	+	+	Still living after 1 1/2 yr, sternal puncture
132		76	F	+	—	—	—	0	131,000	—	65 0	65 0	18 days	—	—	
133		67	M	—	+	+	+	0	21,300	34,450	0 0 80	0 0 80	2 yr	—	—	

until her death. A few days before death marked swelling of the gums, a temperature of 102 F and three small subcutaneous hemorrhages over the legs were noted. Clearly detectable enlargement of the lymph nodes or spleen did not develop, and there was no bleeding from the mucous membranes.

Examination of the blood showed hemoglobin, 74 per cent (10.21 Gm), red blood cells, 3,640,000 and white blood cells, 151,000. The blood smears sent to me for diagnosis showed 65 per cent promonocytes and 4 per cent monoblasts (table 1). A diagnosis of acute monocytic leukemia was made.

The patient died on November 4. Permission for a necropsy was not obtained.

CASE 6—H. S., a man aged 67, entered St. Vincent's Hospital on April 21, 1936, complaining of recurrent nosebleeds, weakness and loss of weight. He had had hypertensive heart disease for many years but was otherwise well until the fall of 1935, when he began to notice loss of weight and became progressively weaker. In March 1936 he began to have recurrent epistaxis, and the bleeding had become progressively more difficult to control. He entered the hospital on April 21 for cauterization of the bleeding areas. He was discharged on April 22 before the report of the examination of the blood made on April 21 was charted. He returned on April 29, in the service of Dr. T. Tharaldsen.⁶ I saw him in consultation shortly after his admission to the hospital. He had a recurrence of epistaxis on April 24, lasting until April 26 and beginning again on April 27. The gums were not swollen, ecchymoses had appeared over the body and there was moderate enlargement of the axillary lymph nodes. The spleen was enlarged to percussion but not palpable. The data for the blood are shown in table 1. The patient was discharged from the hospital on May 6, and died at home on September 14. Permission for necropsy was not obtained.

COMMENT

The data for these cases and those previously reported are summarized in table 2. From this table it is evident that monocytic leukemia is being reported with increasing frequency. Since it is being reported more frequently and since individual investigators are reporting larger numbers of cases (I have seen 6 patients with this disorder in two years), it seems that monocytic leukemia is a more common disease than it has been thought to be. Rosenthal and Harris and Doan and Wiseman found reports of 532 cases of leukemia, from which statistics on the incidence of monocytic leukemia were calculated. From these reports it was estimated that 62.2 per cent were cases of myeloid leukemia, 32.7 per cent were cases of lymphoid leukemia and 5.1 per cent were cases of monocytic leukemia. Rosenthal and Harris have suggested that this relative incidence is about that of the various types of cells in normal blood. If this is correct, from 3 to 9 per cent (Osgood) of all the cases of leukemia should be cases of monocytic leukemia. The great rarity of plasma cell leukemia (Osgood and Hunter) tends to confirm this theory, because plasma cells are only occasionally seen in the blood.

It is evident that monocytic leukemia may occur at any age, the youngest patient reported on being 11 months old and the oldest 78.

⁶ Dr. T. Tharaldsen of Portland, Ore., gave me permission to report this case.

years There was definitely a greater incidence in males (67 per cent) than in females (33 per cent)

Swelling of the gums was one of the most constant features, occurring in 80 per cent of the 88 cases in which the gums were mentioned, and when it is observed it should always lead to a serious consideration of the possibility of monocytic leukemia It was more marked and constant than in other cases of acute leukemia, and a surprising number of the patients consulted a dentist before going to a physician In many instances the swelling was associated with gangrenous stomatitis, similar to that in agranulocytosis, but it may precede the development of infection or may never be associated with infection

Petechiae occurred in 69 per cent of the 80 cases in which they were searched for They were usually associated with bleeding from the mucous membranes, especially of the mouth and nose, as is common in other types of acute leukemia

Enlargement of the lymph nodes was less frequently noted (77 per cent of the 110 cases in which the lymph nodes were examined) than in other types of leukemia

The spleen as a rule was moderately enlarged, being reported as palpable, enlarged to percussion or of definitely increased weight at necropsy in 84 per cent of the 117 cases in which there was a note in this regard In a number of cases the size of the spleen was definitely recorded as normal, so that splenomegaly is not constant in this disease The average weight of the spleen in the cases of adults in which it was recorded was 473 Gm, and the range was from 145 to 1,430 Gm It is evident, therefore, that the usual enlargement is of moderate degree An extremely large spleen in a patient with leukemia favors a diagnosis of myelogenous rather than monocytic leukemia

Enlargement of the liver was almost as common as enlargement of the spleen, being observed in 66 per cent of the 90 cases in which a notation was made The average weight of the liver in the adults in which the weight was reported was 2,047 Gm, and the range of the weight was from 1,250 to 3,240 Gm

Other characteristic clinical findings were pallor, weakness and fever The pallor and weakness were due to the rapidly developing myelophthisic anemia The temperature was usually from 101 to 103 F, occasionally rising as high as 107 F

Other symptoms that were less common but apparently definitely related to the disease were pain in the bones and joints, cutaneous lesions other than petechiae or ecchymoses and tumors consisting of monocytes The cutaneous lesions were of two types One consisted of nodules in the skin which were firm and painless and which on histologic exami-

nation proved to consist largely of monocytes, promonocytes, monoblasts and reticular tissue. This type of cutaneous lesion seemed to be specific for monocytic leukemia and to be different from the infiltrations of myelogenous or lymphatic leukemia. These lesions have been well discussed by Mercer. The second type of cutaneous lesion was staphylococcic infection of the skin, with multiple boils and carbuncles. Furunculosis occurred in these cases more frequently than can be explained by mere coincidence. Our case 4 belonged to this group. In the case reported by Gittins and Hawksley there were bilateral ovarian tumors consisting of monocytes, and in the case reported by Haining, Kimball and Janes a tumor surrounding the rectum produced intestinal obstruction.

The white cell counts in the 124 cases in which they were recorded ranged from 660 to 461,000. The average of the highest counts recorded in each case was 99,600. Three patients were leukopenic throughout the course, 6 showed leukopenia at times and no counts above the upper limits of normal and 6 had only normal leukocyte counts recorded, making a total of 15 cases, or 12 per cent, in which the white cell count was never elevated. In only 65 cases, or 52 per cent, was the leukocyte count consistently elevated.

The differential counts are difficult to evaluate because most authors did not segregate the immature from the mature monocytes. The actual distribution of the cells can be judged only from those reports in which promonocytes and monoblasts were listed, because in most instances in which no figures appeared in these columns many of the cells under the heading monocytes were undoubtedly promonocytes and monoblasts. If the cells were classed in monocytic leukemia as stem cells, myeloblasts or hemocytoblasts, I have arbitrarily placed them in the column marked monoblasts. It is evident, however, that the cells of the monocyte series may vary in the blood from almost none to 99 per cent and that the percentage of immature cells in the monocyte series may vary from practically none to over 95 per cent. In only 2 cases (23 and 94, in table 2) was there a true aleukemic course, with no increase in the number of mature or immature monocytes noted in the blood at any time. In a number of others there were aleukemic phases. Unquestionably more cases of aleukemic monocytic leukemia will be recorded now that sternal puncture (Young and Osgood) is coming into general use as a diagnostic method.

The average duration of the illness in the 104 cases in which it was possible to make a determination from the reports was five and one-fourth months. The shortest duration was ten days and the longest four years. If the cases are divided into those of acute, subacute and chronic involvement arbitrarily, the involvement being called acute when the duration of the illness was six months or less, subacute when

between six months and one year, and chronic when more than one year, there were 80 cases (77 per cent) of acute leukemia, 13 cases (13 per cent) of subacute leukemia and 11 cases (11 per cent) of chronic leukemia. The tendency for monocytic leukemia to run an acute course is clearly evident and is in contrast with that for lymphoid or myeloid leukemia, in which the chronic forms are more common than the acute forms.

ORIGIN OF MONOCYTES

Forkner has listed nineteen different views as to the origin of the monocyte, which clearly show the confusion that exists in regard to the origin of this cell. Undoubtedly this confusion would have been cleared up sooner if more studies of the sternal marrow had been made in cases of this type of leukemia. In our cases in which sternal punctures were made it was evident that the monocyte developed from a cell which may be called the monoblast, similar in morphology to the myeloblast. All intermediate stages (fig 3) between the typical mature monocyte of the blood and this monoblast could be found. As a rule the material aspirated from the marrow consisted almost entirely of these blast cells, and the picture was so widely different from the normal that there could be no question that this cell was the precursor of the monocyte.

The characteristic features of the monoblast are its large size (from 15 to 30 microns in diameter), the fine chromatin structure of the nucleus, similar to that of the myeloblast but perhaps even more transparent, and the uniform presence of nucleoli. The nucleus is usually round or oval. The cytoplasm ranges from basophilic to deeply basophilic, and there is more in proportion to the size of the nucleus than in the myeloblast or the lymphoblast.

Monoblasts are difficult, sometimes impossible, to distinguish from myeloblasts or lymphoblasts. The chief point of difference is the more frequent occurrence of fine, diffuse azurophil granules in the cytoplasm of the monoblast, similar to those of the mature monocyte. Since these granules are not always present in the monoblast and the myeloblast may sometimes contain them, the morphologic appearance of the individual cell is often not adequate to differentiate them with certainty. The peroxidase stain does not assist in this differentiation, as all these cells show a negative peroxidase reaction. However, the fact that some of these cells are morphologically indistinguishable does not prove that they are actually identical, it is often impossible to tell in a smear treated with Wright's stain whether a cell is a promyelocyte type II or a prolymphocyte, but the peroxidase stain clearly shows them to be different.

Most authors have not given any characteristic name to cells intermediate between the mature monocyte of the blood and the monoblast,

while some have used the term promonocyte or premonocyte for these cells, without clearly defining it. I suggest that they be referred to as promonocytes and that a promonocyte be defined as a cell which has the characteristic cytoplasm and diffuse, fine azurophil granules of the mature monocyte, with the same irregularly shaped nucleus, having a finer chromatin structure and showing uniformly the presence of nucle-

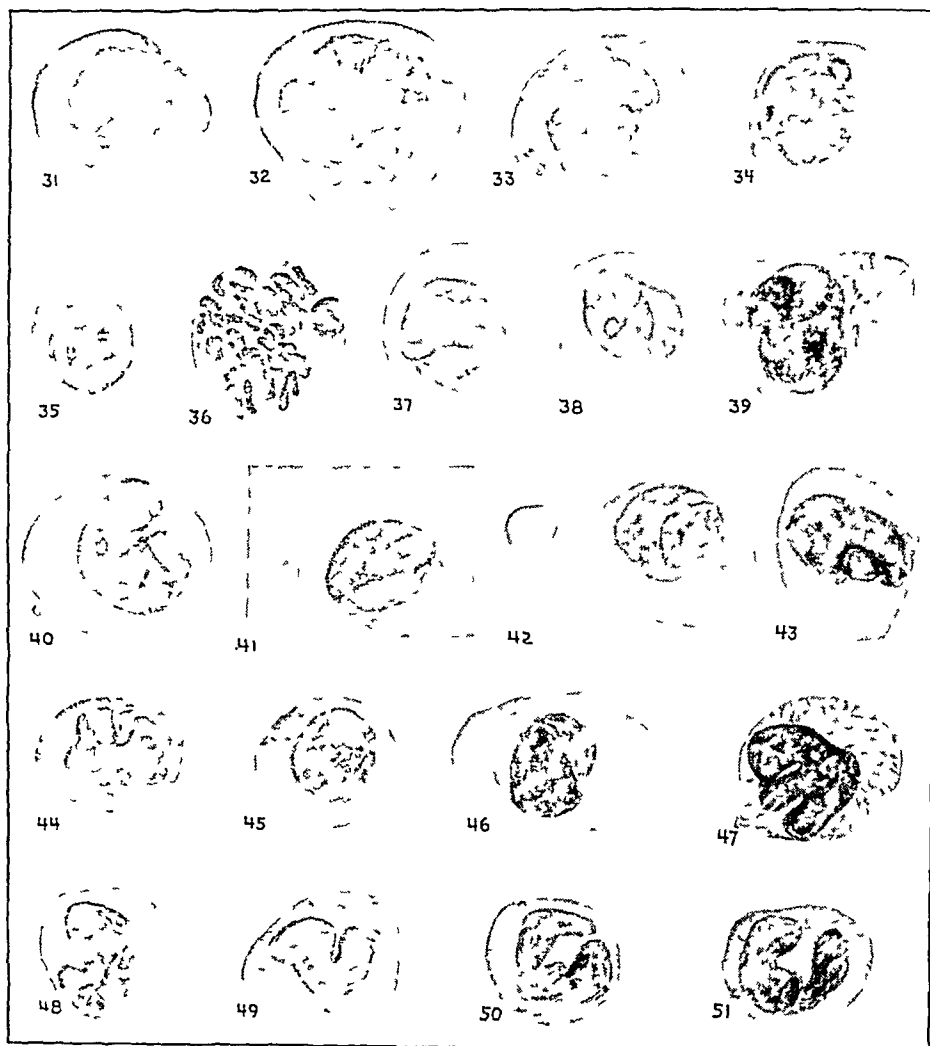


Fig 3—Photographs of the cells of the monocyte series ($\times 1,000$) from the colored illustrations in the "Atlas of Hematology." The original drawings are two and one-half times the size shown here. The numbers correspond to the cell numbers in the atlas: monoblasts, 31 to 33, promonocytes, 34 to 41 (36, a cell in mitosis, 41, a disintegrated promonocyte resembling the hemohistioblast of Ferrata), monocytes, 42 to 51.

oli. As Fowler has pointed out, the nucleus of the promonocyte, with its delicate chromatin network, is often sufficiently transparent so that underlying folds of the nucleus may be seen through it. The presence

of nucleoli constitutes the major point of difference from the normal monocyte of the blood. The presence of truly round or oval nuclei with an extremely fine chromatin structure differentiates the monoblast from the promonocyte. These differences are shown in figure 3 but can be seen much better in cells 31 to 51 in the volume entitled "Atlas of Hematology" by Osgood and Ashworth, in which these cells are shown in color, magnified 2,500 diameters.

The reaction of the monocyte and of the promonocyte to the peroxidase stain varies. Even in the same specimen of blood some monocytes will show a positive reaction and others will show a negative reaction, and in many preparations no cells showing a positive reaction can be found. The most plausible explanation for this is that the monocyte itself shows a negative peroxidase reaction, but, being an extremely phagocytic cell, it frequently takes up from disintegrating granulocytes the material that shows a positive reaction. I have frequently seen this phagocytosis in cultures of marrow (Osgood and Brownlee, Osgood and Muscovitz), and there is no reason to believe that this does not occur in normal blood also.

There is good evidence that the monoblast is capable of forming reticulum, since reticulum has been found in the cutaneous lesions (Mercer) of monocytic leukemia and in the rectal (Haining, Kimball and Janes) and ovarian tumors (Gittins and Hawksley) which have been reported. There is definite evidence from studies of sternal marrow (Young and Osgood) that monocytes are present throughout life in the marrow, and undoubtedly they may be formed in the spleen in fetal life and sometimes during the course of monocytic leukemia. If they were formed normally in the lymph nodes one could expect to see them in considerable numbers in the lymph from the thoracic duct, which is not the case. It is my impression that in the present state of knowledge the terms reticulosis and reticulo-endotheliosis should not be used, as they are misleading and suggest the possession of knowledge that is not at hand. It would be equally logical to call all forms of leukemia reticulo-endotheliosis because all cells of the blood are formed in reticulo-endothelial tissue. I have never been able to find any transition in morphologic studies between the lymphocyte and the monocyte, even in material from the lymph nodes in cases of monocytic leukemia. Although I have been unable to find a method of morphologically differentiating the most immature examples of any one of the blast cells from the others, our studies (Osgood and Ashworth) lead me to believe that the monoblast, the myeloblast, the lymphoblast, the plasmoblast and the megakaryoblast are, in adult life, distinct types of cells, each of which can develop only into a mature cell of its own series. It is possible that cultures of marrow (Osgood and Brownlee, Osgood and Muscovitz) will definitely settle this point.

SUMMARY

Six cases of monocytic leukemia are reported, and reports of 127 other cases are cited from the literature, indicating that monocytic leukemia is a relatively common condition

The clinical and hematologic features of these 133 cases are summarized in table 2. The most characteristic clinical features are the typically acute course, the unusual tendency to swelling of the gums and the frequent association of fever, stomatitis and hemorrhages. The most important hematologic features are the appearance of promonocytes in the blood and of large numbers of monoblasts and promonocytes in the sternal marrow.

Studies of marrow in monocytic leukemia show clearly that the mature monocyte arises from the monoblast in the marrow and develops through the stage of the promonocyte into the mature monocyte of normal blood.

The monoblast and the promonocyte are described and defined.

The term monocytic leukemia is preferable to reticulosis or reticuloendotheliosis.

The cutaneous lesions of monocytic leukemia are described, and the differences from the cutaneous lesions of other types of leukemia are pointed out.

NOTE.—Since submitting this paper for publication I have studied 3 additional cases. Twenty additional reports have been found in the literature and have been included in the bibliography.

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POISONING FROM CUTANEOUS APPLICATION OF IODINE

A RARE ASPECT OF ITS TOXICOLOGIC PROPERTIES

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Iodine was discovered accidentally by Courtois in 1811¹. It was first used as a therapeutic agent by Coindet in 1820 in treating goiter. Its success was so great that it was soon used in many other diseases, but the unfortunate results consequent on the inhalation of the nascent fumes caused it to fall somewhat into disrepute. However, other effective uses were soon discovered. Ricord in 1836 used it in scrofula, Lugol in 1831 used it effectively in tertiary syphilis, and Wallace in 1836 published a report of a series of cases in which potassium iodide in large doses was used in the treatment of syphilis. Bonnet, in 1839, was the first to use iodine as an antiseptic, employing it in various infections, he originated the injection treatment of ovarian cysts. Since that time it has been used widely, and its alcoholic solutions are recognized as some of the most effective of known antiseptics.

Iodine is probably most frequently used in the form of potassium and sodium salts. As such it is employed as an expectorant, as a diuretic, in the treatment of goiter, in the treatment of syphilis, as a contrast medium in urography and in various circulatory diseases in which there is a fibrotic or inflammatory factor, i. e., arteriosclerosis and syphilitic arteritis. The most recent use of the iodides has been in fungous infections. It has been shown that the use of iodides is contraindicated in tuberculosis, presumably because they have a direct action on devitalized, especially fibrotic, tissue and thus may be responsible for the breakdown of protective barriers. Finally, the iodides have been used indiscriminately in a wide variety of conditions, with indifferent results.

Externally, elemental iodine is employed in the form of the alcoholic solution, having long been used, as has been noted, as a cutaneous antiseptic, it is employed also for preoperative sterilization of the skin and as a counterirritant. Other uses, such as to sclerose cysts of various types and as an inhalant (in the nascent form), have largely been abandoned.

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1 Courtois, cited by Sollman, Torald. A Manual of Pharmacology, Philadelphia, W B Saunders Company, 1932

TOXICOLOGIC ASPECT

There are two common conceptions of iodine poisoning first, the poisoning following the ingestion of the tincture in relatively large quantities, and, second, the manifestations which occasionally follow the prolonged administration of the salts, called iodism. Nevertheless, there are, in reality, five methods by which iodine is or has been administered which may result in poisoning. These are (1) the oral ingestion of iodine or its alcoholic solution, (2) the oral ingestion of the salts of iodine, which occasionally results in iodism, (3) the inhalation of the fumes into the upper and lower passages of the respiratory tract, (4) the absorption of the tincture from a cyst into which it has been injected, and (5) the absorption of alcoholic solutions applied to the skin. Of all these, only the first is preponderantly local in its toxic effect, the others are mainly systemic.

The oral ingestion of the tincture is usually carried out with suicidal intent. Immediate gastric uneasiness, vomiting, diarrhea, with occasional bloody stools, and vasomotor collapse¹ follow. These effects are in large part due to the local corrosive action of the iodine on the alimentary mucous membrane, occurring immediately after the ingestion of the solution and allowing scant time for absorption. The fatal dose is supposed to be from 2 to 3 Gm., but much larger doses have been taken with recovery.

Iodism is a nonspecific phenomenon, as entirely analogous effects may follow the use of thiocyanates, nitrates and bromides. The manifestations are as follows:

- 1 Cutaneous manifestations of various sorts, including pustular and bullous eruptions, generalized erythema, purpura, urticaria and vesication—all occasionally accompanied with fever
- 2 Conjunctivitis, laryngitis, bronchitis and rhinitis
- 3 Headache
- 4 Stomatitis
- 5 Anorexia
- 6 Parotitis
- 7 Terminal cachectic states following the prolongation of symptoms and including anemia, emaciation, mental disturbances, etc

The mechanism of these effects is still not satisfactorily explained. Fatal termination is occasionally seen.

For a long time it was thought that the direct contact of nascent iodine with various pulmonary inflammations would be beneficial. Clinical trial resulted in many mishaps, owing probably, as Luckhardt and his associates² proved experimentally, to depression of the blood pressure, with consequent pulmonary edema and respiratory collapse.

2 Luckhardt, A. B., Koch, F. C., Schroeder, W. F., and Wieland, A. H. The Physiological Action of the Fumes of Iodine, *J. Pharmacol. & Exper. Therap.* 15:1 (March) 1920.

The injection of alcoholic solution of iodine into cysts of various sorts was formerly widely practiced but has now been relegated to the limbo of discarded therapeutic measures on account of many accidents which occurred. Rose³ first called attention to this in a report of three cases in all of which systemic reactions were present, one terminating fatally. The fatal case was that of a girl of 16. Into an ovarian cyst a solution containing 5 ounces (150 cc) of tincture of iodine was injected. Immediately after this the patient began to vomit profusely, and she experienced extreme thirst and became cold, with a weak intermittent pulse. Parotitis then developed, associated with a diminution of salivary flow, fever, oliguria and albuminuria. Coma supervened, and the girl died in collapse. Autopsy revealed traces of iodine as iodide in the lungs and bronchi, none was revealed elsewhere. Nothnagel and Rossbach⁴ collected reports of thirty-five fatal cases following the injection of the drugs into cysts.

Systemic toxic manifestations following the use of alcoholic solutions of iodine on the skin and mucous membranes are undoubtedly extremely rare, considering the widespread use of this antiseptic. Peterson and Haines⁵ stated "When applied by surgeons freely to absorbing surfaces, it [iodine] may cause systemic disturbances, such as headache, dizziness, mental trouble with gastric symptoms brought out indirectly." Search of the literature reveals reports of only fourteen cases of systemic or remote cutaneous disturbances, the case presented herewith being the fifteenth. Undoubtedly there have been other cases, and probably they will become more infrequent with the increasing use of other cutaneous antiseptics at the expense of iodine. That local reactions may occur after the application of the tincture to the skin is well known, Herzog⁶ having described many cases of dermatitis from its use in wounds in war time. However, Rutherford⁷ noted only three cases in a total of 14,000 cases, one patient showing local ecchymosis and two showing bullae.

Iodine applied to the skin and mucous membrane is absorbed as iodide. Luckhardt and his colleagues² showed that the liberal application of the tincture to the skin resulted in the excretion of 4.71 mg of

3 Rose, E. Das Jod in grosser Dose, *Virchows Arch f path Anat* **35** 12 (Jan) 1866

4 Nothnagel, H, and Rossbach, M. J. *Nouveaux elements de matiere medicale et de therapeutique*, Paris, J.-B. Bailliere & fils, 1889, quoted by deBroe¹¹

5 Peterson F, and Haines, W. S. *Legal Medicine and Toxicology*, Philadelphia, W. B. Saunders Company, 1923, vol 2, p 167

6 Herzog, W. Zur Anwendung der Jodtinktur, *Munchen med Wchnschr* **61** 2319, 1914

7 Rutherford, W. J. Excessive Reaction Following the Use of Tincture of Iodine, *Brit M J* **1** 846, 1915

iodide in the urine during the following twenty-four hours. The systemic effects are probably due to iodide, as Buschke and Ollendorff's⁸ patient showed a generalized eruption following the local application of iodoform, sixteen years later a similar eruption appeared after the ingestion of potassium iodide. These considerations are borne out when the symptoms of the patients who have been affected systemically by local applications are considered, but all such systemic manifestations must occur in patients who are extremely hypersensitive to iodine or who have become sensitive to it, as the quantity absorbed through the skin is relatively minute.

REPORT OF A CASE

E. H., a 52 year old man, was admitted to the medical isolation unit of the New Haven Hospital on April 4, 1936, complaining of a cold.

Three weeks prior to his admission to the hospital the patient began to experience headache, malaise, chilly sensations and pain in the chest. He began also to have a cough productive of small amounts of greenish yellow sputum which was often blood streaked. The pain was in the right anterior portion of the chest and was pleuritic. The patient believed he had three bouts of fever but had had no night sweats. Anorexia had been severe, and he had lost about 20 pounds (9 Kg.) since the onset of his illness. He became progressively weaker and finally came to the hospital for relief.

The family history was unimportant, there had been no tuberculosis in the family. The patient had married but had separated from his wife, who was living and well. There were three children living and well.

The past history was essentially unimportant. The patient had been unemployed and homeless for four years. He could remember having had only an occasional cold or sore throat. He had never had a cough previous to the onset of his present illness. He had been a house painter intermittently for thirty-five years but was fully cognizant of the dangers of working with lead and had never had a symptom of poisoning.

Physical examination revealed a well developed but rather emaciated man, who appeared to be mildly and chronically ill. The temperature was 102 F., the pulse rate 90, the respiratory rate 24 and the blood pressure 90 systolic and 65 diastolic. The skin was warm and dry and was fairly dark. There was no eruption. The head, eyes, ears and nose were normal. The teeth were discolored and carious, many were missing. The pharynx was not injected. There was no cervical adenopathy. The trachea was in the midline, the thyroid gland was small and smooth. Examination of the chest revealed diminished respiratory expansion on the right side. Over the upper half of the right side of the chest there were dulness, bronchovesicular breathing and a few coarse râles. A loud friction rub was heard in the right axilla during respiration. The heart was not remarkable. The abdomen was scaphoid, and there was moderate voluntary spasm in the right upper quadrant. The genitalia were normal. Rectal examination revealed no abnormality. The reflexes were all normal. The extremities were not remarkable. There was no generalized lymphadenopathy.

⁸ Buschke, A., and Ollendorff, H. Zur Kenntnis der Jodidiosynkrasie der Haut, *Deutsche med. Wchnschr.* **51** 2109, 1925.

The laboratory findings were as follows Examination of the blood showed 4,200,000 erythrocytes, 70 per cent (Sahl) hemoglobin, 7,000 leukocytes, 70 (14 nonsegmented) polymorphonuclears, 24 lymphocytes, 3 large mononuclears, 3 eosinophils and 0 basophils The urine was clear, yellow and acid, with a specific gravity of 1.022 and no albumin or sugar The sediment showed a rare white blood cell per high power field The sputum was yellow and purulent, from 5 to 20 acid-fast bacilli being seen per high power field The stools were dark brown and solid and contained no gross blood or mucus The reaction to guaiac was negative The Kahn test was negative Chemical analysis of the blood showed nonprotein nitrogen, 32 mg per hundred cubic centimeters, carbon dioxide, 28.4 milliequivalents, chlorides, 87.1 to 93.9 milliequivalents, total proteins, 7 Gm per hundred cubic centimeters, albumin, 3.44 Gm, globulin, 3.56 Gm, and sodium, 125 milliequivalents

A roentgenogram of the chest showed extensive pulmonary tuberculosis of the upper and middle lobes of the right lung, with probable cavitation of the upper lobe, and beginning tuberculous infiltration of the left lung

Course and Treatment—The patient was put to bed immediately and for the next few days was merely kept under observation During this time he was constantly febrile, the temperature ranging between 99 and 103 F He was given $\frac{1}{2}$ grain (0.03 Gm) of codeine sulfate when necessary for his cough

In view of the patient's asthenia, hypotension and dark skin, the question of Addison's disease was considered, for a short time studies of the blood were made, including determinations of the sodium and chloride contents, and subsequently large doses of sodium chloride were given However, this caused no change in the patient's symptoms, and studies of the blood revealed normal values for sodium and only a slight reduction of the chloride content

Ten days after his admission to the hospital it was decided that artificial pneumothorax was the most suitable therapy⁹ The cutaneous preparation for pneumothorax therapy is usually performed as follows an area varying from 10 to 20 cm in diameter is covered with full strength tincture of iodine U. S. P., and the iodine is then removed with 70 per cent alcohol There is, naturally, some variation in the amount of iodine removed, and occasionally a fair amount remains on the skin

Between April 16 and 29 the patient received six pneumothorax treatments, a total of 2,950 cc of air being introduced, causing the right lung to collapse to roughly its former size Immediately after each treatment the patient felt much worse, and in each case the temperature rose suddenly from 1 to 3 F No physical change was demonstrable

On April 30, the day following the sixth pneumothorax treatment, the patient's temperature rose from 100.4 to 102 F, and there was a slight reddening of the skin over the area prepared with iodine The next day there was an extensive, confluent rash over the entire back, and on May 2 the entire body was covered with a morbilliform eruption that was confluent over the back The mucous membranes were clear, the patient felt no worse than usual He had been receiving codeine, this was stopped By May 3 the rash had faded, and it was gone the

9 The isolation unit of the New Haven Hospital does not include a permanent sanatorium for tuberculous patients Patients with tuberculosis are admitted only before the diagnosis is made or in an emergency and remain there pending their transfer to a state or federal sanatorium Since vacancies in these sanatoriums are occasionally scarce, patients sometimes must wait as long as three months If pneumothorax is indicated immediately, it is instituted while the patient is in the isolation unit

next day Another pneumothorax treatment was given on May 5, only alcohol being used for the cutaneous preparation, and codeine was resumed with no adverse results On May 11 at 3 p m another pneumothorax treatment was given, and iodine again was used for the preparation of the skin That night the temperature rose to 104 F, the pulse rate was 120 and on the following morning there was a generalized morbilliform eruption The area of skin which had been prepared was fiery red The rash elsewhere was maculopapular and pink, being confluent in some areas Culture of blood taken at this time was sterile There was moderate generalized lymphadenopathy The mucous membranes of the mouth and eyelids were injected and covered with a thick yellow mucoid exudate There was no bulbar conjunctivitis Over the soft palate a hemorrhagic eruption was seen Irrigations of the throat and eye washes were instituted The patient was nauseated and took fluids poorly A hypodermoclysis of 1,500 cc was given

On the next day, May 14, the rash was everywhere confluent, the extremities were swollen and painful to the touch There was a thick purulent discharge from the eyes, and a profuse flow of viscid, mucoid saliva drooled from the mouth The patient was lethargic and coughed up large amounts of greenish watery sputum There was a leukocyte count of 14,000

On May 15 the patient's condition was slightly worse The superficial layers of the skin on the back began to peel off in large sheets

On May 16 the patient was disoriented There was beginning desquamation of the extremities, which were swollen, cyanotic and painful The conjunctival and the oral discharge were more profuse Urine at this time showed a 2 plus reaction for albumin, and the sediment contained from 3 to 5 white blood cells and 1 or 2 red blood cells per high power field The leukocyte count was only 7,650 All fluid was given parenterally The patient became much worse during the night On the morning of May 17 the skin was peeling from the body in large sheets, leaving great denuded areas which exuded serum, so that the bed was constantly wet Speech was thick, and coma became progressive There was incontinence of urine and feces There was, however, marked oliguria The nonprotein nitrogen content at this time was 38 mg per hundred cubic centimeters The patient's condition rapidly became worse, Cheyne-Stokes respiration was present and in spite of appropriate stimulating measures the patient died

Postmortem Examination—The autopsy was performed the following day by Dr Robert Tennant The anatomic diagnosis was (a) primary extensive exfoliative dermatitis, exfoliative pharyngitis, tracheitis, esophagitis, glossitis and acute bronchitis, (b) secondary bilateral chronic ulcerative and proliferative pulmonary tuberculosis, bilateral fibrous pleural adhesions, air in the right pleural cavity (artificial pneumothorax) and tuberculous ulcer of the cecum

The summary of the protocol is as follows

The body was that of a well developed but poorly nourished man The weight of the body was 44 Kg, and the length was 173 cm

There was extensive exfoliative dermatitis over all parts of the body The superficial layers of skin were denuded, leaving large gray-red granular surfaces Around the face and mouth a dark yellowish green material, which appeared to be a mixture of serum and fibrin, was adherent There was exudative material over the entire body, the back was practically denuded of epithelium In regions where the skin was not removed there was a diffuse macular rash, the macules being red and smooth The eyelids were glued together with a yellow-green mucoid exudate, which covered the face The conjunctivae were reddened There was pus at the external nares and on the lips The body was emaciated, there being practically no subcutaneous fat There was no adenopathy

On section the peritoneum appeared normal over the visceral surfaces. The spleen was enlarged. There was no fluid in either pleural space. The right lung was partially collapsed, fibrous adhesions binding portions of it to the wall of the chest. The left lung was intact, but an occasional firm nodule could be palpated. The pericardium was smooth and contained 10 cc of clear fluid.

The heart weighed 237 Gm and was normal grossly and microscopically.

The left lung had some fibrous adhesion over the pleural surface, over which appeared a few small, deeply pigmented scars. The cut surface was red and crepitant, and red fluid oozed from it. The bronchial mucosa was deep red.

The right lung showed many adhesions over the pleural surface. The cut surface showed an empty cavity, 5 cm in diameter, in the apex. This had a fairly thick fibrous wall which was surrounded by several sharply demarcated yellow caseous nodules, about 0.5 cm in diameter, several of these were seen in the middle and lower lobes also. At the anterior margin of the middle lobe there was a uniformly consolidated caseous mass, 5 cm in diameter. About a third of the right lung showed tuberculous involvement, there was practically none in the left lung.

Microscopic sections of the wall of the cavity showed dense fibrous connective tissue, throughout which conglomerate tubercles with caseous centers could be seen. Throughout other portions of the right lung many conglomerate caseous tubercles were seen, associated with the bronchi. Sections of the middle lobe showed a necrotizing, caseous tuberculous process.

The tracheal mucosa was desquamated. The surface was covered with fibrin and polymorphonuclear leukocytes, and the blood vessels were distended with red blood cells. The mucous glands were swollen.

The spleen weighed 237 Gm, and the malpighian corpuscles were large and numerous. The stomach, duodenum, pancreas and gallbladder were normal.

The liver weighed 1,653 Gm. The surface was smooth. In several small foci that were examined microscopically the cells were necrotic and were infiltrated with lymphocytes. The total weight of the adrenal glands was 19 Gm. They were normal.

The kidneys weighed 173 and 176 Gm, respectively. There was slight cloudiness of the cortical markings, but microscopically the glands appeared normal. The testes were normal.

Examination of the brain, a small portion of the spinal cord, the rectum, the ureters and the aorta revealed no abnormality.

In the cecum there was one solitary ulcer, 3 by 0.5 cm, with slightly raised edges and a yellow granular base. Sections showed infiltration with monocytes and a few polymorphonuclears. Immediately below the base of the ulcer was a tubercle.

The superficial layers of the esophageal mucosa had desquamated and formed a cast in the lumen, this had a cooked appearance. The remaining mucosa desquamated easily, leaving a granular, reddened surface. A similar process extended into the pharynx. The tongue showed some evidence of superficial desquamation. The mucosa of the pharynx and trachea were deep bright red. There was no ulceration, but there was a yellow exudate over a few points on the surface.

Microscopically the mucosa of the tongue was almost entirely denuded. In a few places it was intact but necrotic and infiltrated with polymorphonuclear leukocytes. The submucosal blood vessels were distended with red blood cells, and the connective tissue was infiltrated with polymorphonuclear leukocytes, lymphocytes and monocytes.

Sections of the esophageal mucosa showed it to be completely desquamated, the microscopic picture of the submucosal tissue was similar to that seen in the tongue. The thyroid and parathyroid glands were normal.

Microscopic sections of the skin showed complete denudation of the epithelium, with only a few scant sheaths remaining in various areas. In some regions the superficial layers remained but appeared lifted up in blister-like formation. In the corium there was a scant, diffuse infiltration of cells, mainly lymphocytes and polymorphonuclear leukocytes, with an occasional eosinophil. In areas where the epithelium was still attached, it appeared as a pink-staining layer in which the cellular outline was barely visible.

REVIEW OF THE LITERATURE

As has been mentioned previously, there have been few cases reported in which toxic symptoms followed the cutaneous application of iodine in alcoholic solution. The cases which have been reported may be summarized as follows:

Culpeper's¹⁰ case, which was reported in 1888, was the first one that could be found. A child of 11 suffering from eczema (?) of the legs had 2 drachms (8 Gm.) of tincture of iodine applied. There was immediate local pain, followed in twenty-four hours by lumbar and generalized pain, abdominal pain and diarrhea. A starch test showed that the stools contained iodine. (This is evidently an error, since iodine is absorbed and excreted solely as iodide.) There was no fever, but diarrhea was progressive, the stools becoming practically pure blood by the fifth day. There were anuria, priapism and extreme vertigo without mental confusion. The patient died six days after the application.

The next two cases are those cited in the textbook of Stokvis¹¹ and by Bioe¹⁴. These patients had an extensive pruritic eruption and severe iodism following small local applications of an alcoholic solution of iodine, the symptoms including coryza, edema, dyspnea, headache and syncope, which persisted for several days.

The next two cases were reported separately by Bielsalsky¹² and by Moszkowicz¹³ at the annual meeting of the German Surgical Congress in 1911. In both the symptoms followed the use of tincture of iodine as a cutaneous preparation for Forster's operation (section of several dorsal roots). Severe suppurative dermatitis developed, and the patients died. No further details were given in the reports.

10 Culpeper, W. O. Acute Iodine Poisoning, *Therap. Gaz.* (sect. 3) **4** 225, 1888.

11 Stokvis, B. J. *Leçons de pharmacothérapie*, Paris, O. Doin, 1905, p. 213, quoted by deBroe¹⁴.

12 Bielsalsky. Foerster'sche Operation, *Verhandl. d. deutsch. Gesellsch. f. Chir.* **39** 34, 1910.

13 Moszkowicz, L. Foerster'sche Operation, *Verhandl. d. deutsch. Gesellsch. f. Chir.* **39** 40, 1910.

deBroe¹⁴ in 1911 wrote a review of these cases, including in it a hitherto unreported case of an unnamed medical officer and a case of his own. In the former case tincture of iodine (this was the preparation mentioned in the French pharmacopeial "Codex," and contained 10 per cent free iodine) had been applied to the knee for some minor complaint. The application was followed by fever, malaise, delirium and "symptoms of peritonitis," all of which lasted forty-eight hours.

Broe's own case is of great interest. The patient was a healthy soldier on whom inguinal herniorrhaphy was performed, 10 per cent tincture of iodine being used in the preparation of the skin. The day following the operation, which had been uneventful, the patient had a slight cough and a few coarse râles in the chest. An iodine dressing was applied to the chest as a counterirritant. During the following night the patient began to have intense itching of both sites where iodine had been applied (the operative site had been cleaned with alcohol after the application of iodine). On the second postoperative day there was brilliant erythema of the itching areas, which extended beyond the borders of the sites to which iodine had been applied. Slight fever, conjunctivitis and lacrimation were present. Soothing dressings were applied, but the erythema spread rapidly, moderate desquamation began to appear over the sternum. The patient became thirsty. The conjunctivitis and lacrimation became more intense, the patient began to make convulsive movements which necessitated restraint, the stools became loose and there was incontinence. The temperature rose to 40.3 C (105 F), divergent strabismus appeared, the patient became comatose, dyspneic and cyanotic, and death occurred on the third postoperative day. Autopsy revealed, besides the cutaneous lesions mentioned, some pulmonary congestion, splenomegaly and slight hepatomegaly, the liver weighing 2,500 Gm.

Happel¹⁵ in 1921 reported a case of somewhat different type but one in which an extreme idiosyncrasy was shown. A woman of 50, after supravaginal hysterectomy, had less than 1 drop of tincture of iodine applied to the cervical stump for purposes of cautery, seventeen hours after the operation the patient had intense itching and burning of the skin and swelling of the face and hands. When she saw wheals on her body she said, "They used iodine on me." The nurse told her that a trinitrophenol preparation had been used on the skin, but the patient insisted that iodine had been used somewhere, saying that she had had a similar experience nine years previously after the application of tincture

14 deBroe, Patris. Intoxication iodique mortelle consecutive à l'emploi de la teinture d'iode pour la sterilisation pre-operatoire de la peau, *Arch de med et pharm mil* 57 96, 1911.

15 Happel, H. E. A Case of Unusual Susceptibility to Iodine, *J A M A* 76 1164 (April 23) 1921.

of iodine to her neck. The rash was a generalized urticaria, which was quickly relieved with small doses of epinephrine.

Bryan¹⁶ reported the case of a man of 52 who had an abdominal operation. The skin was prepared with half-strength tincture of iodine. Twenty-four hours later an urticarial rash, moderate anemia and cerebral symptoms developed, and the patient was moderately toxic. Recovery was complete, but it was found later that his life had been despaired of on a previous occasion, after the application of iodine to an infected arm.

Rowell¹⁷ in 1923 reviewed several cases and reported the case of a man aged 55. Half-strength tincture of iodine had been used to prepare the skin for laparotomy and hemorrhaphy. On the afternoon of the day of operation the patient's temperature and pulse rate rose, and he began to show signs of shock. On the first postoperative day fever and moderate shock persisted. He improved slowly for the next few days, his temperature falling, but on the fifth postoperative day he was much worse. The areas to which iodine had been applied had become purple, and these lesions slowly spread. The temperature rose, the patient became incontinent and hemorrhagic blebs began to appear on the extremities. The stools became watery. On the eighth postoperative day the skin of the entire abdomen was purple, and blebs were more numerous on the legs and feet. The patient became irrational and died on the ninth postoperative day, just before death purple petechiae appeared over the face and thorax. The urine was normal. Progressive anemia and marked leukocytosis were noted. Chemical analysis of the blood revealed no abnormality. The clotting time was between six and seven and one-half minutes. The autopsy showed essentially no abnormality, except for an adenocarcinoma of the stomach with local metastasis.

Clifford¹⁸ saw a patient who, after the application of tincture of iodine to the wrist and forearm, showed local erythema and vesication, but this was followed by a scarlet urticarial erythema of the face and neck. The lesions all disappeared, but the reapplication of iodine months later to a cut finger caused vesication and the formation of bullae on the hands and arms bilaterally, with erythema of the right pectoral region.

Galli¹⁹ in 1929 reported on a woman aged 27 who had had tincture of iodine applied to the shoulder, with sudden and dramatic results. A

16 Bryan, R. C. One Hundred Prostatectomies, *Virginia M. Monthly* **48**: 338, 1921, personal communication to Rowell¹⁷.

17 Rowell, H. G. The Surgical Importance of Iodine Idiosyncrasy and Poisoning, *Surg., Gynec. & Obst.* **36**: 219 (Feb.) 1923.

18 Clifford, S. H. Iodine Hypersensitization, *Boston M. & S. J.* **195**: 931 (Nov. 11) 1926.

19 Galli, A. Intossicazione acuta per applicazione percutanea di tintura di jodio, *Gazz. d. osp.* **40**: 1299 (Oct. 6) 1929.

TABLE 1—Data in Cases of Iodine Poisoning

Author	Age, Years	Sex	Preparation of Iodine Used	Site of Application	Time Elapsing Until Symptoms Appeared	Type of Eruption	Involve-ment of Mucous Membranes	Constitutional Reaction	Duration of Reaction	Associated Illness	Outcome	Autopsy Observations
Culpeper ¹⁰	11	F	Tincture	Both legs	24 hr	None		Umbilical, generalized, bloody stools, priapism, anuria, vertigo	6 days	Edema of legs	Fatal	
Stokvis ¹¹			Alcoholic solution			'Extensive pruritic'	Iodism	Dyspnea, headache, edema, coryza, syncope	Several days		Recovery	
Stokvis ¹¹			Alcoholic solution			'Extensive pruritic'	Iodism	Dyspnea, headache, edema, coryza, syncope	Several days		Recovery	
Trench medical officer ¹⁴		F	Tincture	Knee		None	None	Fever, malaise, delirium, "symptoms of peritonitis"	48 hr		Recovery	
Bielsalsky ¹²	Child		Tincture	Back		Suppurating dermatitis					Fatal	
Moszkowicz ¹³			Tincture	Back		Suppurating dermatitis					Fatal	
de Broe ¹⁴		M	Tincture	Inguinal region, chest	About 12 hr	Pruritic erythema	Mainly conjunctivae	Fever, conjunctivitis, lacrimation, convulsive movements, diarrhea, strabismus, incontinence, terminal dyspnea and cyanosis	3 days	None	Fatal	Splenomegaly, hepatomegaly, pulmonary congestion
Happel ¹⁵	50	F	Tincture, 1 drop	Cervical stump	17 hr	Generalized urticaria	None	None	2 days	None, post operative hysterectomy	Recovery	

Bryan 16	52	M	Tincture, half strength	Abdomen	24 hr	Generalized urticaria	None	Anuria, cerebral symptoms, moderately toxic	Postoperative prostatectomy	Recovery
Rowell 17	55	F	Tincture, half strength	Abdomen, inguinal region	6 to 10 hr	Hemorrhagic purpura with bleb formation	None	Fever, shock, diarrhoea, irrational	Carcinoma of stomach	Fatal
Clifford 18			Tincture	Wrist and forearm		Scarlet urticarial erythema	None	None		Recovery
Gall 19	27	M	Tincture	Shoulder and chest	Less than 5 min	Generalized punctate erythema	Injection of conjunctivae, coryza, genital swelling	Nausea, vomiting, headache, malaise, precordial pain, dyspnea, cough, coma	More than 3 days	Recovery
Alexander 20	37	M	3-5% alcoholic solution	Inguinal region	24 hr	Local hemorrhagic eruption	None	Liver, tachycardia, delirium	Postoperative herniorrhaphy	Death
Brenas and Wels 21	1	F	Tincture	Umbilicus	15 hr	Brilliant local erythema, spreading, bullae	None	More than 3 days	Coiling of umbilicus	
Seymour	52	F	Tincture	Chest, posterior axillary region	24 hr	Generalized erythema, interfollicular dermatitis	Extensive	Fever, severe coryza, delirium, cyanosis, coma, incontinence	Pulmonary tuberculosis	Fatal
										Pulmonary tuberculosis, exfoliative dermatitis, splenomegaly, pharyngitis, bronchitis, etc

violent burning occurred at the site of application, and within less than five minutes the patient became nauseated and vomited. She had a violent headache, malaise, precordial pain, dyspnea and cough and experienced a sense of impending death. When Galli saw her she was comatose and dyspneic and was vomiting involuntarily, her pulse was weak and thready. After appropriate stimulation and removal of the excess iodine with alcohol, the patient slowly recovered. Three days later redness and swelling of the conjunctivae and the pharyngeal and buccal mucous membranes were noted. There was cervical and axillary lymphadenopathy. A punctate erythema covered the entire body, and there was swelling and redness of the external genitalia, especially the urethral meatus. The patient slowly recovered. The urine was shown to contain iodide. The patient had never previously used iodine in any form.

Alexander²⁰ reported the case of a 37 year old woman who had cutaneous preparation of 2.5 per cent iodine in alcohol twenty-four hours before hemiorrhaphy was performed and again at the time of operation. On the first postoperative day some itching and redness of the prepared area were noted. On the second day the entire area was purple, with an occasional white spot. The temperature rose to 103 F and the pulse rate to 140. The patient became delirious and died on the third day postoperatively. The urine and stools were normal, and leukocytosis was slight. There was, presumably, no autopsy.

Brenas and Weis²¹ reported a case in which tincture of iodine had been applied to the oozing umbilicus of a 4 year old child. Within a few hours violent erythema appeared which spread rapidly, and within three days extensive erythematous and bullous lesions covered the entire abdomen, the chest and the inner aspect of the thighs. No mention was made of systemic disturbances.

COMMENT

The application of tincture of iodine to the skin can hardly be called a hazardous procedure, since the incidence of systemic reactions is apparently low. However, the symptoms and signs of systemic reaction, once they appear, are strikingly similar, as shown in table 1. Many of the case reports presented are, unfortunately, lacking in many essential details, but a tabulation of the available data is presented in table 2.

It may be seen that in most cases ordinary tincture of iodine was employed. The U. S. P. tincture contains 7.5 per cent free iodine, but some foreign preparations contain 10 per cent.

20 Alexander, R. C. Fatal Dermatitis Following the Use of Iodine Spirit Solution, *Brit. M. J.* **2**: 100 (July 19) 1930.

21 Brenas and Weis, quoted by Bory, L. Les iodides cutanées, *Progres med.*, June 23, 1934, p. 1046.

The lapse of time before systemic reactions appear is apparently less than twenty-four hours. In one case (Galli) they appeared immediately, this patient evidently had a real hypersensitivity to iodine, and her symptoms were those of acute anaphylactic shock, followed by symptoms of iodism and a cutaneous rash. Rowell's case probably falls in this same class. In the remaining cases the lapse of time between application of iodine and systemic symptoms was greater, however, although the immediate reaction was not as pronounced, the subsequent reaction was apparently as severe as in the others.

TABLE 2—*Tabulation of Data*

	No of Cases	Percentage
Preparation of iodine employed		
Full strength tincture	10	
Half strength tincture	2	
Alcoholic solution, strength not specified	3	
Time elapsing before systemic symptoms appeared		
Immediately	1	
Up to 6 hours	2	
Up to 12 hours	1	
Up to 24 hours	5	
Over 24 hours	0	
Not specified	6	
Types of eruption		
Urticarial	4	
Erythematous	4	
Hemorrhagic or purpuric	2	
"Suppurative"	2	
Exfoliative dermatitis	1	
None	2	
Involvement of mucous membranes	5	33
Principal symptoms		
Delirium	9	
Fever	5	
Diarrhea	4	
Pain	3	
Headache	3	
Edema	3	
Terminal symptoms		
Dyspnea	4	
Incontinence	2	
Oliguria or anuria	2	
Cyanosis	2	
Mortality rate		46.9

Two of the cutaneous rashes were definitely urticarial, two were specified as being merely pruritic, and four were erythematous, one of the latter was pruritic. The urticaria is suggestive of an "allergic" type of sensitivity, whereas the erythemas are of the type commonly associated with drug sensitivity. The two purpuric rashes were definitely suggestive of iodide reaction. Unfortunately, the rashes termed "suppurative" are not explained in detail.

The case reported in this paper is the only one in which one of the severest, if not the most severe, types of cutaneous reaction was noted, namely, exfoliative dermatitis. Whether this reaction was due to the

iodine-tuberculosis relationship is an interesting question Lass²² demonstrated that the intracutaneous administration of a solution of sodium iodide to normal subjects caused no reaction, whereas nine of fifteen patients with pulmonary tuberculosis so tested showed local reddening and wheal formation. The reason given for the avoidance of iodides in tuberculosis is that the iodides facilitate lysis of the tissue formed by inflammatory reaction, thus facilitating the spread of the tubercle bacilli, but Lass' work and the case of exfoliative dermatitis presented seem to indicate that there may be other factors which must be taken into consideration. The fact that the patient with exfoliative dermatitis did not show any reaction to iodine until several applications had been made suggests that sensitivity was being established which finally manifested itself in severe cutaneous and systemic disturbances.

In five of the fifteen cases coryza was associated with iodism, thus making it conclusive that the reaction was due to iodine. As has been stated previously, these persons must have been extremely sensitive, as the total minimal dose of iodine in the form of potassium iodide required to produce symptoms of iodism is from 60 to 75 grains¹ (3.8 to 4.8 Gm.), and in these persons milligram quantities were used.

To attempt to explain the symptoms and signs in these cases would be entering the realm of pure speculation. The usual explanation of the cause of death when large doses of iodide have been employed is that the iodide alters the colloidal equilibrium of the blood. That explanation is not tenable in the cases presented here, as the concentration of iodide in the blood stream must have been relatively minute. I believe that in the present case death was attributable to the exfoliative dermatitis.

SUMMARY

A case is presented in which there were several local and general cutaneous manifestations and severe systemic symptoms, including iodism, following repeated local applications of tincture of iodine to the skin, and which terminated fatally after the development of exfoliative dermatitis.

A survey of available literature shows reports of fourteen cases of hypersensitivity to cutaneous applications of an alcoholic solution of iodine to the skin. Toxic manifestations were cutaneous and systemic. The mortality rate was 46.9 per cent.

²² Lass, E. Jod- und Histaminempfindlichkeit der Haut bei Tuberkulosen, *Ztschr. f. Tuberk.* 67:350, 1933.

CHRONIC RELAPSING LATENT MENINGEAL PLAGUE

K F MEYER, M D, P H D

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AND

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SAN FRANCISCO

Plague has become a permanent problem in the western states¹ In fact, the investigations of 1935 and 1936 have conclusively shown that the endemic reservoir in the ground squirrel (*Citellus beecheyi*), first suspected in 1904 and proved in 1908 in California,² now embraces large territories and new species of rodents (*Citellus oregonus*, *Citellus armatus*, *Citellus columbianus*, *Citellus grammurus*, *Citellus richardsoni*, *Marmota flaviventris*, *Eutamias quadrivittatus* and *Cynomys parvidens*) in Oregon, Idaho, Nevada, Utah and Montana Renewed interest created by the discovery of extensive and destructive epidemics among squirrels in the foothills of the Sierra Nevadas and the recesses of the Warner Mountains in northeastern California in 1934 has doubtless been responsible for the recognition of a few cases of plague in human beings These infections must be interpreted as accidents, as they involve occupational groups or vacationists who have in one way or another come in contact with animals Thus, a sheep herder, who in 1934 was employed on a desert near Lakeview, Ore,³ contracted bubonic plague In 1935 a 10 year old boy in California and a 7 year old boy in Utah had bacteriologically proved "pestis minor infections" of the axillary lymph nodes after handling brush rabbits or squirrels Another case of plague in a veterinarian is interesting from an epidemiological point of view, since the sources of *Pasteurella pestis* have not been conclusively established, although newer knowledge indicates a much wider distribution of infected fleas than was formerly anticipated It is our purpose in this communication not to discuss the many riddles

From the George Williams Hooper Foundation and the Department of Pathology and the Department of Pediatrics, the University of California Medical School

1 Meyer, K F, and Eddie, B California & West Med **43** 399, 1935

2 Wherry, W B J Infect Dis **5** 485, 1908

3 Levin, William Northwest Med **34** 161, 1935

which the problem of plague in wild rodents—ylvatic plague—offers in its relations to man but to present the history of a patient with chronic bubonic plague with latent meningeal localization and death on the one hundred and twenty-first day after onset and isolation of fully virulent *P. pestis* from the brain and its coverings. In all probability the boy contracted the infection while playing in an area in which rodent plague was epizootic. The history briefly is as follows:

REPORT OF A CASE

History—C. P., a boy aged 10 years and 5 months, was admitted to the University of California Hospital on Oct. 15, 1934. He died on October 22. The chief complaint was fever, anorexia and vomiting of one week's duration after convalescence from bubonic plague.

The family history was essentially unimportant.

The patient lived on a ranch about 5 miles (8 kilometers) north of Porterville, Calif. On June 1 the family went to a ranch 10 miles (16 kilometers) beyond White River in the Posey Creek country, which is in a plague area. On June 19 the boy complained of being ill with nausea and vomiting, he had a high fever and was delirious at times. No diagnosis could be made by the local physician who saw him at that time. On June 20 the fever continued to be high. He was still irrational at times and complained of double vision. He was considerably troubled with mucus in the throat and some pains in the right shoulder.

About noon on June 21 he was brought home and put under the care of Dr. Walter W. Tourtellott. At that time the temperature was 104° F. The patient seemed confused mentally and had definite diplopia, a rapid, thready pulse and a normal respiratory rate. He complained chiefly of pain in the shoulder, particularly in the axillary region. The right axillary fossa was fuller than the left, and a large painful node (the size of a walnut) was palpated. It was definitely tender. The reflexes were normal and equal. There was no suggestion of a Kernig sign or stiffness of the neck. There was no rash of any sort. The throat was reddened, and the tongue was coated. No other physical findings were noted except possible hoarseness. During the day, with forcing of fluids and flushings, the fever subsided somewhat, and it seemed that the general condition improved. The boy was given 50 cc. of whole blood from his father, on the assumption that the disease might be anterior poliomyelitis.

When seen at 1 p. m. on June 22 the boy did not seem to be acutely ill. He was entirely rational, and there was nothing unusual about his voice. The fever was slight (the temperature being 100 or 101° F.), and the quality of the pulse was good. He was perspiring moderately, but owing to the weather this probably was not unusual. Casual inspection revealed no difficulty in breathing, no signs of rash or injury and nothing unusual except a tendency to protect the right axilla and limit the motion of the right arm. The reflexes were normal, and there were no signs of muscle weakness. The right axilla bulged slightly, and a few small nodes (the size of a pea) could be palpated. The axillary region was still tender. The subaxillary, anterior and posterior cervical, left axillary and inguinal lymph nodes were not palpable. On the right cheek at the angle of the mandible a small lesion, apparently an insect bite, was noted. The boy said that a "kissing bug" had bitten him there about a week previously. Blood smears were made, and blood for culture and agglutination was taken.

On June 24 the boy's temperature rose to over 105 F. On June 25 it was over 106 F, and on the morning of June 26 it reached 107.6 F rectally, with a septic swing. Even with the high fever the boy was only mildly confused. Dehydration was not marked. The appearance of the right axilla had changed considerably. The skin presented a reddened brawny induration, and the underlying tissues were tense, swollen and exceedingly tender. The patient cried out with every movement of the right arm. The cervical lymph nodes on both sides were swollen, tense and painful.

A blood count made at that time in a local laboratory showed 20,000 leukocytes, with 95 per cent polymorphonuclears, 64 per cent hemoglobin and 3,450,000 erythrocytes. A blood culture in dextrose broth also was made, and as the boy was raising some thick mucus, a specimen of sputum was examined.

On June 27 Dr. W. H. Kellogg, chief of the bureau of laboratories of the state department of public health, reported that he had succeeded in isolating a pure culture of the plague bacillus from the blood cultures.

The swelling under the arm receded at first and then became more noticeable, the edema extending down the side. On June 29 redness developed along the tendons of the biceps, and the abscess opened spontaneously, exuding a thick, gelatinous pus. Smears of this pus were nearly solid with *P. pestis*. This bubo continued to discharge until about September 1, when it healed. The nodes in the neck receded without suppuration. No enlargement of the spleen or liver was evident at any time.

At the end of about three weeks (on July 16) the child again became severely ill (fig. 1) and complained of a stiff neck and pain in the back. He had a headache, and the Kernig sign was present. He became unconscious. Spinal puncture showed 105 leukocytes, with 80 polymorphonuclear cells. At that time smears and cultures were sterile. During this period the boy was given saline and dextrose solution intravenously and rectal feeding. He gradually improved until September 13, when the temperature became lower and he was sitting up in bed, eating well and gaining weight. On September 13 the quarantine was raised, and the nurses were dismissed. The patient still had a low grade septic temperature, but the improvement was so marked that it was felt that the danger of contagion had passed and that the parents could care for him.

During the first week of October (October 8) he again became acutely ill. This attack was characterized by a high temperature, delirium at times, vomiting, headache in the frontal and suboccipital region and rigidity of the neck.

On entrance to the hospital, eight days later, he was emaciated and showed marked tremor of the hands and feet, fibrillary muscle twitching, marked hyperesthesia and extreme pallor. There were sores on the gums, slight general lymphadenopathy, healed scars in the right axilla and healed areas over the back. The heart and lungs were essentially normal, and the spleen was palpable just below the costal margin. All the deep reflexes were hyperactive but apparently equal. There were unsustained clonic ankle movements, generalized ataxia of the hands and slight cervical stiffness, and there seemed to be definite mental confusion, with, at times, complete aphasia.

Laboratory Data—Tests showed that the blood of the patient was of type II, that of the father, of type II, and that of the mother, of type IV. The blood of the parents was compatible.

On October 20 examination of the spinal fluid revealed that it was yellow and under increased pressure. It contained 425 cells, with 84 per cent lymphocytes, and

the Pandy reaction was 4+. Direct smear showed short gram-negative rods. On October 21 there were 352 cells, with 82 per cent lymphocytes, and the Pandy reaction was 4+. A smear showed the same organisms as had the previous specimen.

When the patient was admitted a blood count showed hemoglobin, 98 per cent, erythrocytes, 6,590,000, leukocytes, 11,900, with neutrophils 70 per cent, eosinophils 2 per cent, basophils 1 per cent, small lymphocytes 11 per cent, large lymphocytes 5 per cent, large monocytes 6 per cent and myelocytes 6 per cent. On October 17 a blood count showed hemoglobin, 95 per cent, erythrocytes, 4,990,000, and leukocytes, 13,800, with 94 per cent neutrophils. The blood serum in a dilution of 1:320 agglutinated a strain of *P. pestis* (in a solution of formaldehyde).

Chemical analysis of the blood showed carbon dioxide content of the plasma, 62.5 volumes per cent, plasma chlorides, 553.41 mg per hundred cubic centimeters, serum calcium 10.6 mg, and serum phosphorus, 3.14 mg. Urinalysis revealed no abnormality.

Treatment—Transfusions, continuous intravenous injection of dextrose, clyses and sedatives were employed.

Course—The patient was in a critical condition on entry and in spite of symptomatic therapy continued to fail, having periods in which his condition seemed to be improving but after which he would again lapse into unconsciousness. Although he was afebrile for the first few days, his temperature continued to rise and reached 41.5 C (106 F) at the time of death on October 22, one hundred and twenty-one days after the onset of the illness.

Gross Postmortem Examination—The autopsy was performed four hours after death. Only the significant observations will be given here.

Skin The skin over the back, especially in the lumbar region, was marked by numerous small scars resembling healed abscesses. There were scars likewise in the right axilla.

Lymph Nodes The mesenteric lymph nodes and other lymph nodes throughout the body were essentially of normal size.

Spleen The spleen was moderately enlarged, weighing 200 Gm. It was dark blue-gray and soft, with rounded edges. The cut surface was red and mushy, and considerable pulp could be scraped off with a knife. Except for purulent bronchitis and early bronchopneumonia, the only other pathologic condition, in addition to that in the spleen, was in the brain.

Brain The dura was tense, and the convolutions were markedly flattened, indicating that there had been marked intracranial pressure. The pia-arachnoid was thickened and opaque, particularly in the region of the pons, the inferior portion of the cerebellum and the base of the cerebrum. The lateral and third ventricles were markedly distended with cloudy, slightly yellowish fluid. A thick gelatinous exudate was attached to the walls of the lateral ventricles. The choroid plexuses were particularly reddish gray, soggy, swollen and covered with an exudate similar to that in the other portions of the ventricles. The aqueduct of Sylvius, below the level of the superior colliculus, appeared to be occluded by white and somewhat granular tissue resembling the exudate in the ventricles. The fourth ventricle contained numerous small punctate hemorrhages. The spinal cord, below the medulla, appeared to be normal.

The significant gross features, therefore, were the moderate enlargement and softening of the spleen and the intense swelling of the brain, due to internal

hydrocephalus and ventriculitis, with the exudate in the pia-arachnoid at the base. In addition, the bone marrow of the femur was dark red and hyperplastic. The lymph nodes had returned to normal size.

Microscopic Postmortem Examination—Spleen The spleen throughout had the appearance of early autolysis, resembling to some extent an infarcted spleen, that is to say, the cells and tissue in general did not stain as normal cells should. The splenic corpuscles were remarkably small, and the lymphoid cells comprising them were scattered for some distance into the pulp. The sinusoids were markedly distended with red blood cells and contained an increased number of monocytes and polymorphonuclear cells. The pulp, in general, was definitely increased. The change was not marked enough to be typical of acute plague, but there was a definite resemblance. It looked like an early rather than the late change one might have expected.

Brain Sections from the cortex showed moderate cellular infiltration into the meninges, and in places these cells followed the blood vessels into the cortical tissue. Sections from the lateral ventricle showed marked cellular infiltration beneath the ependyma. Many of these cells were young mononuclear cells resembling lymphocytes, others were macrophages, and a few polymorphonuclear cells were seen. Adjacent to the ventricular wall there was marked necrosis of the cortical tissue, associated with macrophage infiltration and round cell accumulations around the blood vessels (fig 2). A section of the choroid plexus showed remarkable infiltration with the same types of cells described, with a thick exudate on the surface of the plexus (fig 3). Other sections showing the pons, aqueduct of Sylvius and fourth ventricle indicated that the infection had passed throughout the ventricular system and in all places had infiltrated beyond the surface of the ependyma. Everywhere there was the necrosis described in the neighborhood of the lateral ventricle. The most pronounced meningitis was in the region of the pons and cerebellum.

Bacteriologic Postmortem Examination—Culture of material from the axillary lymph nodes was sterile. Culture of pulp from the spleen showed five colonies of cocci. The heart blood was sterile. Culture of bronchial mucous parenchyma showed staphylococci, streptococci and diphtheroid bacilli.

Spinal fluid removed from the right ventricle and centrifugated showed sediment on blood agar slants. There were numerous gram-negative bipolar, pleomorphic rods. Pure culture of the spinal fluid was agglutinated by *P. pestis* antiserum and biochemically behaved like *P. pestis*.

A guinea-pig inoculated percutaneously with culture lost weight. When killed on the seventh day the animal showed left inguinal and iliac buboes and several metastatic lesions in the liver and spleen. Culture revealed *P. pestis*.

The choroid plexus was emulsified in broth (10 per cent) and injected subdurally into two guinea-pigs (left side). The first animal showed left hypopyon, a loss in weight and anorexia. It was killed on the thirteenth day and showed leptomeningitis, left hypopyon, submaxillary, cervical and left axillary buboes, and metastatic nodules in the lungs, spleen and (one only) liver. *P. pestis* was isolated bacteriologically and culturally from the brain, eye and lymph nodes. The second guinea-pig showed typical plague marasmus. It was killed on the seventeenth day and showed cervical, submaxillary and auricular buboes, leptomeningitis and metastatic nodules in the spleen (two only) and liver (one only). Cultures of material from the lesions yielded a few colonies of *P. pestis*.

The strain of *P. pestis* isolated from the meninges of this patient when passed by the cutaneous route fatally infected guinea-pigs in four or five days. In

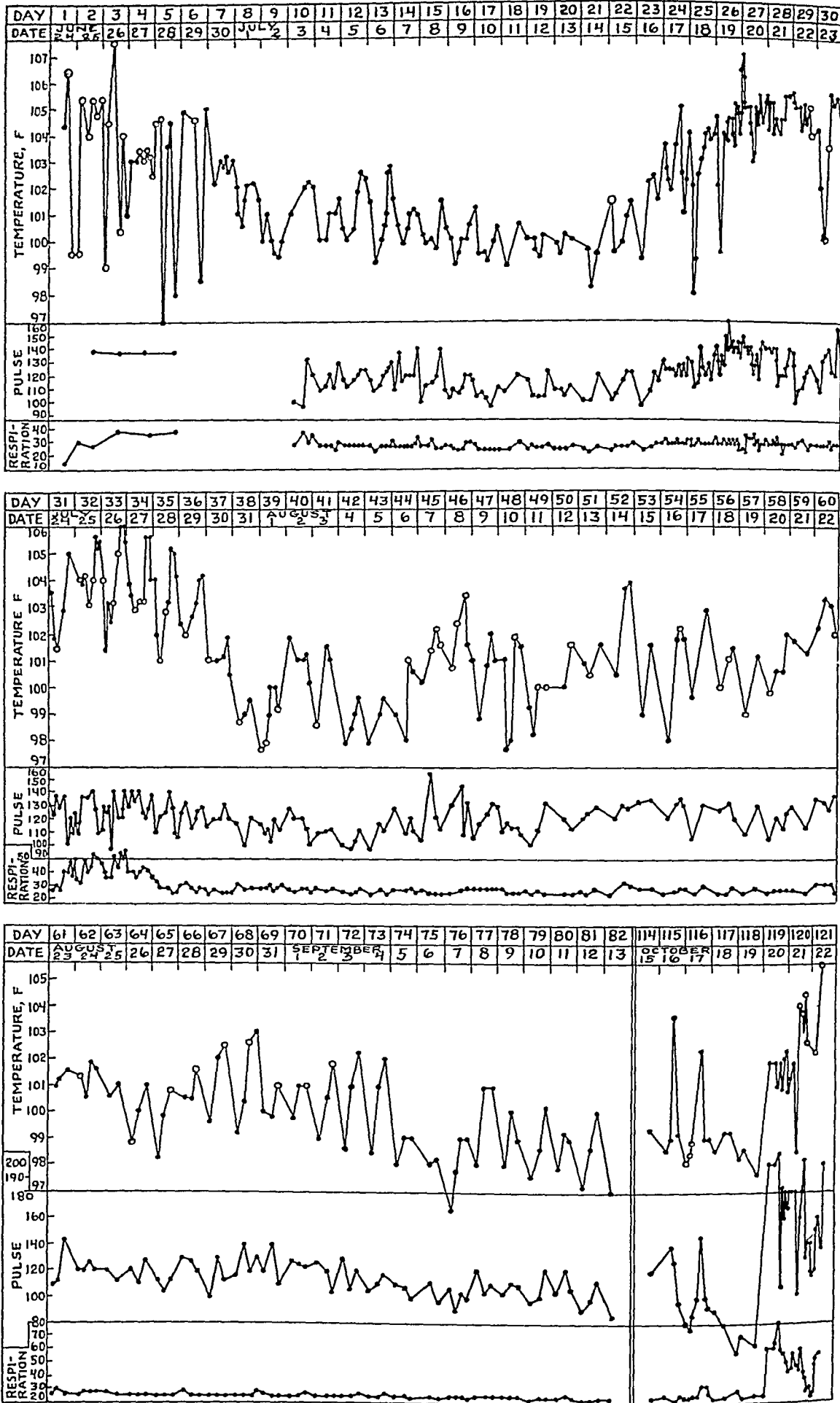


Fig 1—Clinical record of C P, aged 10 years, of Tulare County, Calif, who had bubonic plague. From September 13 to October 15 no record was available. The black dots in the graph for the temperature indicate oral readings, and the circles indicate rectal readings.



Fig 2—Photomicrograph showing the ependymal surface and subependymal tissue of the lateral ventricle. Most of the ependymal cells have sloughed away, and cellular infiltration and necrosis of the underlying tissue and perivascular accumulations of cells as in acute encephalitis are noted.



Fig 3—Photomicrograph of the remarkably thick exudate in the choroid plexus of the lateral ventricle.

comparison with other cultures of *P. pestis* of squirrel origin, the human strain possessed an average degree of infectiousness

Diagnosis—In view of these observations the following diagnosis is fully justified chronic bubonic plague of a secondary latent meningeal type contracted through a flea bite while the patient was near White River (Posey Creek) some time between June 5 and 18, 1934

COMMENT

In the past in the clinical and anatomic descriptions of plague the disease process has been classified, according to mildness or severity, as *pestis minor*, *pestis major* and *pestis siderans* or *pestis fulminans*. Cases of *pestis minor* included cases in which there was mild involvement, always ending in recovery, while cases of *pestis major* comprised those of severe *pestis fulminans*, with a rapidly fatal course. The classification now adopted is one which is based more or less on the particular system of the body invaded by the plague bacillus. Thus, plague is reported as bubonic, septicemic and pneumonic, according to whether the glandular, circulatory or respiratory system is involved. In addition, a description of the carbuncular, intestinal and cerebral types is given sometimes in order to stress certain pronounced systems. After all, these classifications are based on artificial descriptions, representing merely different signs or degrees of one disease, all the cases including main features of a common likeness. In 70 to 80 per cent of cases buboes are noted, and provided an adequate sample of blood is taken, the plague bacillus may be demonstrated in the circulatory system. On the other hand, in a septicemic type pneumonia may develop and become septicemic or bubonic or both. It must be emphasized that there are few diseases which present a greater variety of manifestations than plague. As it may show variations from a mild to a severe attack, from a prolonged illness to death within a few hours or from a malady accompanied with great mental aberration to one with many of its diagnostic symptoms absent, there is frequently difficulty in realizing at first that a patient is suffering from infection with *P. pestis*. For descriptive purposes plague may be clinically divided into plague with buboes and plague without buboes. Again, this distinction is not accurate, since in all forms of plague the lymphatic system is more or less affected, and although this may not be recognized during life, it is invariably observed post mortem. Frequently superadded to the symptoms peculiar to the several varieties of plague are disorders of the nervous system, notably paralysis of the vagus and recurrent nerves. Aphasia, ataxia, dementia and hysterics are most common, and although they are generally temporary, they may become permanent. Signs of meningismus due to an increase in the spinal fluid pressure have frequently been reported. As early as 1899 Calmette and Salimbeni called attention to the clinical dis-

inction between the occasional nervous symptoms caused by the toxins of *P. pestis* which accompany all forms of plague except the most mild and those induced by the direct localization of the organism in the meninges or in the brain substance. They fully corroborated the previous observations of Griesinger⁴ and others made on patients with pronounced psychic symptoms but no actual cerebral infection. A perusal of the available histories on plague leaves no doubt that true meningitis is rare. Moreover, when the condition has been found, it has been acute, and the infection has not lasted for longer than one month. The following case reports, presented chronologically, are available.

The Austrian Commission (Albrecht, Ghon and Muller⁵) reported on a series of 80 clinical cases (with 48 autopsies) in which there was 1 case of plague meningitis.⁶

A 35 year old Hindu was admitted to the hospital on the tenth day of illness. He was free from headache or stiffness of the neck. On the twelfth day clonic twitching and a disturbed sensorium developed. Death occurred on the fifteenth day. Examination of the brain revealed a clumped purulent exudate in the vicinity of the pons and on the surfaces of the cerebellum. The meninges were edematous and dull. The ventricular fluid was turbid with yellowish flakes, and the thickened plexuses were covered with a greenish yellow exudate. The brain substance was soft and sparsely studded with hemorrhages. Plague bacilli were demonstrated bacteriologically and by culture.

The German Indian Plague Commission⁷ (1897), in a series of 376 histories, listed 4 cases in which there was meningeal localization of *P. pestis*.

CASE 1—A 16 year old boy died on the third day of illness with meningitis. At autopsy the dura was tense, and hemorrhages were present. The veins of the meninges were filled with blood, and in the region of the frontal lobes they were embedded in turbid whitish yellow gelatinous fluid. The brain was covered with cell-rich bloody material. The basal ganglions were dark gray-red. In the pons and medulla were large petechiae, and the ventricular surfaces were injected.

CASE 2—A woman of 30 died on the twenty-second day of illness. Separation of the meninges revealed a cell-rich exudate. The organisms were isolated in culture. The dura was tense. The sinuses were filled with dark violet blood. The inner surface of the dura was shiny, and the pia mater was congested. This was also the case with all the blood vessels. The lateral ventricle supplied about 30 cc of yellowish serum. The choroid plexus was pale red.

CASE 3—A 13 year old girl died fifteen days after the onset of illness. At autopsy essentially the same lesions were noted as in the other cases.

4 Griesinger, W, in Virchow, R. *Handbuch der speciellen Pathologie und Therapie*, Erlangen, F. Enke, 1857, vol 2, p 217.

5 Die Beulenpest in Bombay im Jahre 1897, *Denkschr d k Akad d Wissensch Wien* (pt 1) 66 122, (pt 2) 287, 1898.

6 Footnote 5, pt 1, pp 122 and 197, pt 2, p 287.

7 Bericht über die Thatigkeit der zur Erforschung der Pest im Jahre 1897 Indien entsandten Kommission, *Arb a d k Gsundtsamte* 15 16, 1899.

CASE 4—Meningitis and encephalomeningitis were present in this case. Only the anatomic diagnosis was made. The age of the patient, the duration of the illness and other details were not given.

Calmette and Salimbeni⁸ recorded 3 cases, 2 accompanied with meningitis and 1 with meningo-encephalitis.

CASE 1—A woman with meningitis entered the hospital on the seventh day of illness and died two weeks later. At autopsy the lesions at the base in the meninges were in the nature of a fibrinous exudate in the process of organization. In the exudate rare organisms were observed, but culture gave many colonies.

CASE 2—A child aged 7½ years entered the hospital on the second day of illness with a right inguinal bubo. There were all the characteristic symptoms of meningitis—opisthotonos, strabismus, dilatation of the pupils, delirium, cramps in the tendons of the arms, flexion of the limbs and fibrillary movements of the muscles of the face. This patient was treated with serum, and ten days later the buboes were incised. Perfect recovery followed.

CASE 3—A man of 25 entered the hospital with a right inguinal bubo. He was in a wildly delirious state which necessitated control by force. The next day and night there were hallucinations of sight and hearing, and he was unable to recognize friends. The next night he fell into a comatose state and died. At autopsy generalized meningo-encephalitis was present. The subarachnoid spaces were severely affected and contained many plague bacilli. The gray as well as the white substance of the cortex was greatly congested. There was mild edema of the entire cerebrum.

In a series of 16 autopsies Durck⁹ noted 1 case of primary plague pneumonia associated with fresh purulent leptomeningitis. Lafont, Lecomte and Heckenroth^{9a} examined a native of Dakar, French West Africa, who had been picked up unconscious. The spinal fluid consisted of thickropy purulent yellow exudate teeming with plague bacilli. The patient died twenty-four hours after entrance into the hospital. The careful report by Crowell¹⁰ on 75 autopsies details the histories of the following cases of plague meningitis.

CASE 1—An 18 year old boy was said to have been ill for a month. Autopsy revealed cervical retropharyngeal buboes, bronchopneumonia, acute parenchymatous degeneration of the viscera and acute splenitis. The description of the brain is given verbatim: "The meninges over the hemisphere are dry, and the convolutions are flattened. At the base of the brain, about the circle of Willis and ventral to the pons, is found considerable greenish-yellow pus. The lateral ventricles contain a turbid, slightly greenish fluid mixed with a thick, stringy, greenish-yellow pus, which is adherent to the floor of the ventricles, especially at the region of the

8 Calmette, A., and Salimbeni, A. T. *Ann Inst Pasteur* **13** 865, 1899.

9 Durck, H. *Munchen med Wchnschr* **49** 550, 1902.

9a Lafont, A., Lecomte, A., and Heckenroth, F. *Bull Soc path exot* **8** 92, 1915.

10 Crowell, B. C. *Philippine J Sc* **10** 301, 1915.

choroid plexus, which is completely enveloped in the exudate. The floors of the ventricles are thickly covered by this shaggy mass. The third and fourth ventricles contain a slightly turbid fluid."

CASE 2—A 19 year old girl had been ill for two weeks. At death the anatomic diagnosis included acute suppurative lymphadenitis (primary bubo) of the right axilla, acute ependymitis and leptomeningitis, acute degeneration of the kidneys, liver and spleen, chronic fibrous pleurisy and pregnancy of six months. The description of the brain was as follows: "The cerebral leptomeninges contain a slight excess of fluid which appears slightly turbid. On opening the right lateral ventricle, it is found to contain a considerable amount of yellowish-gray pus. The choroid plexus is large and soft. The left choroid is smaller, but also surrounded by grayish exudate. The fourth ventricle is apparently free. The brain substance is pale and shows nothing abnormal."

In both these cases the organisms were cultured from the exudate in the ventricles.

Uriarte¹¹ observed a patient with iridocyclitis and hypopyon of one eye due to *P. pestis*. Death occurred suddenly in the third week of illness. At autopsy the meninges were observed to be covered with small abscesses containing the plague bacillus in pure culture. According to Paso,¹² a 39 year old Spaniard suffering from inguinal and submaxillary bubonic-septicemic plague showed signs of meningitis. Despite intensive treatment with antiplague serum (80 to 120 cc), he died on the fifteenth day, and *P. pestis* was demonstrated in the turbid spinal fluid.

The most recent report on plague meningitis was made by Montagne and Rivoalen.¹³

An 8 year old child entered the hospital at Dakar, French West Africa, with an axillary bubo on July 8. After the administration of antiplague serum, the enlargement of the node disappeared, but on July 17 nervous symptoms were noted. The Kernig's sign was present, there were incessant movements of the hands and eyeballs and spasms of the masseter and left sternocleidomastoid muscle became apparent. The first lumbar puncture and blood culture yielded no organism, while the second puncture, taken on July 20, yielded flaky fluid containing *P. pestis*. The diagnosis of plague meningitis was confirmed at autopsy on July 21, the thirteenth day after the onset of illness.

The mere demonstration of *P. pestis* in the spinal fluid at autopsy without gross anatomic changes should not be considered as evidence of plague meningitis. Wu Lien-Teh¹⁴ in a study of 1,921 cases of primary plague pneumonia noted congestion of the meninges and occasional studding of the brain substance with hemorrhages. The spinal fluid was clear, but as a rule positive bacteriologic observations were made

11 Uriarte, L. *Compt rend Soc de biol* **91** 1039, 1924

12 Paso, J. R. *Semana med* **32** 1139, 1925

13 Montagne, M., and Rivoalen, A. *Bull Soc path exot* **29** 21, 1936

14 Wu Lien-Teh. *A Treatise on Pneumonic Plague*, Geneva, 1926, p. 217

Although the majority of the autopsies that have been reported dealt with patients who succumbed during the acute stage of plague, between the second and the eighth day, it is noteworthy that meningitic involvement was most frequently recorded for patients who survived from the tenth to the twentieth day of the infection. The longest duration of illness was twenty-eight days. In the case under consideration the meningitic localization of the plague process took place in the third week of the disease and persisted in a latent stage for over one hundred days. It is therefore by no means surprising to find a patient in a state of typical plague marasmus, a complication which usually ends in death. This chronic type of plague is claimed to be caused by secondary pyemic infections in which various streptococci and staphylococci play a part. Neither the gross anatomic observations nor the bacteriologic examination of the organs of our patient was suggestive of secondary infection. The marasmus therefore must be attributed to the toxins of the plague bacillus.

Until recently the clinical descriptions have conveyed the impression that plague, with a mortality of from 50 to 75 per cent in the purely bubonic form and of from 75 to 100 per cent solely in the pneumonic form, rarely if ever appears as a chronic infection. The early observation by Choksy¹⁵ and the Austrian Commission,¹⁶ that the plague bacilli may be present in an active state in iliac buboes or in the spleen for forty-eight and fifty-two days, respectively, is rarely mentioned. It is a well known fact that the pus of buboes may contain plague bacilli in an active state one or two months after the onset of the disease (Dujardin-Beaumetz and Joltrain,¹⁷ Leger and Lhuerre¹⁸ and Tanon and Cambessedes¹⁹). Gotschlich²⁰ said he isolated the bacilli from the sputum of a patient on the seventy-sixth day of illness, forty-two days after he had risen from his bed. In 1914 Ilvento and Mazzitelli²¹ and in 1922 Léger and Baur²² established the important fact that healthy afebrile persons living in an endemic plague area may harbor virulent *P. pestis* in small noninflamed lymph nodes. Even more interesting are the reports by Durand and Conseil,²³ who found the bacteria in the

15 Choksy, N. H. Some Observations on Plague and Its Treatment with Lustig's Serum, *Indian M. Rec.* **20** 353, 1901, *J. Trop. Med.* **4** 106, 1901.

16 Footnote 5, p. 532.

17 Dujardin-Beaumetz, E., and Joltrain, E. *Bull. et mem. Soc. med. d. hop. de Paris* **44** 1739, 1920.

18 Leger, M., and Lhuerre. *Bull. Soc. path. exot.* **15** 759, 1922.

19 Tanon, L., and Cambessedes. *Rev. de med. et d'hyg. trop.* **15** 65, 1923.

20 Gotschlich, E. *Ztschr. f. Hyg. u. Infektionskr.* **32** 402, 1899.

21 Ilvento, A., and Mazzitelli, M. *Riforma med.* **30** 348, 1914.

22 Leger, M., and Baur, A. *Bull. Acad. d. sc.* **175** 734, 1922.

23 Durand, P., and Conseil, E. *Arch. Inst. Pasteur de Tunis* **16** 92, 1927.

lymph nodes two and twelve months, respectively, after complete recovery or four and fourteen months, respectively, after the onset of the plague. In a more recent article Durand²⁴ has reported that he isolated the microbes from an inflamed and painful inguinal lymph node seventeen months after the patient had with the aid of antiplague serum recovered from acute bubonic plague.

Influenced by the studies of the French worker, Nikanorow²⁵ punctured the lymph nodes of 4 healthy persons who had been in intimate contact with plague patients. The axillary nodes of 1 contained virulent plague bacilli.

In view of these reports it is obviously proved that a patient not only in the acute but also in the chronic stage of plague, regardless of the severity of the infection, or an apparently healthy person who has been in contact with the infective agent may be a carrier of virulent plague bacilli for a long time. The history of our patient not only adds another interesting report to the ever increasing series of observations on latent plague but forcibly indicates the progressively important need for studies of sylvatic plague and its relation to man. One cannot escape the impression that the recent cases of plague in the western states merely reflect the behavior of an agent which causes mild infections with a tendency to latency. Nothing is known regarding subclinical infections, yet it is surprising to note that the persons who for nearly twenty years have manned the field investigation laboratories in California and have been continuously exposed to infected fleas and highly infectious rodents have remained absolutely free from plague. When the opportunity arises their susceptibility to *P. pestis* will be evaluated by cutaneous phagocytic and serologic tests.

Finally, from an epidemiological point of view it may be pertinent to ask these questions: Can a patient with chronic meningeal plague spread the infection? What is the rôle of the human carriers of *P. pestis*? The French and Russian investigators have maintained that latent bubonic plague may serve as a reservoir and under certain conditions perpetuate the infection by human agency alone. In order to be infective, a patient with latent plague not only must harbor the bacilli in the lymph nodes or the meninges but must also have bacteremia. Durand said he believed that intercurrent infections, such as influenza, measles, etc., may induce a flaring up of the process and that the human flea would then assume the rôle of the vector. At present no evidence has been obtained to support this theory. In fact, there is every reason to believe that, just as in rodents with chronic lesions, in human beings

24 Durand, P. Arch. Inst. Pasteur de Tunis **20** 77, 1931.

25 Nikanorow, S. M. Seuchenbekämpfung **4** 140, 1927.

with latent plague the disease ends blindly and breaks the chain of the infection. However, this deduction should not include another frequently drawn conclusion that *Pulex irritans* may be ignored in the causation of certain outbreaks of plague. The interhuman spread of bubonic plague is a decided possibility, but neither convalescent nor healthy carriers are at all likely to be responsible for the appearance of the disease in the absence of a rodent epizootic. These conclusions guided the public health authorities in permitting the termination of the quarantine measures for our patient and his transference from an infected to a noninfected area.

PHOSPHATASE ACTIVITY, INORGANIC PHOSPHORUS AND CALCIUM OF SERUM IN DISEASE OF LIVER AND BILIARY TRACT

A STUDY OF ONE HUNDRED AND TWENTY-THREE CASES

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An increase in the phosphatase activity of the blood of patients with jaundice was first noted by Roberts¹ in 1930. In a subsequent study of fifty-two cases, Roberts² found that the phosphatase level was consistently and markedly elevated in patients with obstructive jaundice, whereas in patients with toxic and catarrhal jaundice the values were only slightly raised or within normal limits. Roberts concluded that by determining the phosphatase activity of the blood, jaundice of the obstructive type could be distinguished readily from toxic, infective and catarrhal jaundice.

Subsequent investigators have confirmed the finding of an increase in the phosphatase activity of the blood in jaundice due to obstruction of the extrahepatic biliary tract, both in patients³ and in experimental

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A preliminary report appeared in the proceedings of the American Society for Clinical Investigation (*J Clin Investigation* **15** 466, 1936).

1 Roberts, W M. Variations in the Phosphatase Activity of the Blood in Disease, *Brit J Exper Path* **11** 90, 1930.

2 Roberts, W M. Blood Phosphatase and the van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, *Brit M J* **1** 734, 1933.

3 (a) Armstrong, A R, King, E J, and Harris, R I. Phosphatase in Obstructive Jaundice, *Canad M A J* **31** 14, 1934. (b) Greene, C H, Shattuck, H F, and Kaplowitz, L. Phosphatase Content of the Blood Serum in Jaundice, *J Clin Investigation* **13** 1079, 1934. (c) Auston, B, and Coggi, G. La phosphatase du plasma dans différentes affections, *Presse med* **42** 1594, 1934. (d) Herbert, F K. The Plasma Phosphatase in the Various Types of Jaundice, *Brit J Exper Path* **16** 365, 1935. (e) Anderson, R G. The Plasma Phosphatase in Jaundice, *St Barth Hosp Rep* **68** 221, 1935. (f) Fliessinger, N, and Boyer, F. La phosphatase plasmatique en pathologie hépatique, *Rev méd chir mal du foie* **10** 137, 1935. (g) Rothman, M M, Meranze, D R, and Meranze, T. Blood Phosphatase as an Aid in Differential Diagnosis of Jaundice, *Am J M Sc* **192** 526, 1936.

animals,⁴ and the validity of this observation is generally accepted. In jaundice due to hepatitis, however, the results of determinations of blood phosphatase recorded by different observers vary widely. Bodansky and Jaffe,⁵ Greene, Shattuck and Kaplowitz,^{3b} and others⁶ have found marked increases in the phosphatase activity of the blood in hepatitis so frequently as to invalidate the claim that the determination is of value in differentiating this type of jaundice from jaundice due to obstruction of the common duct. Herbert,^{3d} Armstrong, King and Harris^{3a} and others,⁷ however, have found normal or moderately increased values for blood phosphatase in most cases of hepatitis, high values in such cases occurring only occasionally. These workers have concluded that while the overlapping of values in the several types of jaundice limits the usefulness of the determination in differential diagnosis, the method is nevertheless of value.

These inconsistencies arise, in part, from the use of methods for estimating phosphatase activity that are so different as to preclude a direct comparison of results. (The results, moreover, are expressed in a variety of units.) There are, in fact, difficulties in the way of even a relative comparison of values obtained by Kay's original method with those derived by Bodansky's method, particularly in the higher ranges. In some instances, furthermore, investigators using the same method have reported different values for the range of normal variation,⁸ and these differences must be considered when comparisons of the results in cases of jaundice are attempted. Values for phosphatase activity of children and adolescents with catarrhal jaundice⁵ have been accepted as markedly elevated, although the values reported are in part below or only moderately above the normal maximum for the respective age groups. It appears, also, that there are important differences in the systems of classification of jaundice employed by various investigators, and it is further apparent that opinions diverge as to the adequacy of evidence necessary for definitely establishing the cause and type of jaundice. There is, finally, the difficulty that while a sharp distinction is drawn between obstructive jaundice and catarrhal jaundice or hepatitis for diagnostic purposes, it is probable that in the latter disorders obstruction also plays a rôle. And, as Herbert^{3d} pointed out, varying

4 Bodansky, A, and Jaffe, H. L. Phosphatase Studies. VIII. Increase of Serum Phosphatase After Bile Duct Ligation in Dog, *Proc Soc Exper Biol & Med* **31** 1179, 1934. Armstrong, King and Harris^{3a}. Fiessinger and Boyer^{3f}.

5 Bodansky, A, and Jaffe, H. L. Phosphatase Studies. IV. Serum Phosphatase of Non-Osseous Origin, Significance of the Variations of Serum Phosphatase in Jaundice, *Proc Soc Exper Biol & Med* **31** 107, 1933.

6 Cantarow, A. Review of Phosphatase Activity and of Calcium and Electrolyte Metabolism, *Internat Clin* **46** 230, 1936. Fiessinger and Boyer^{3f}.

7 Auston and Coggi^{3c}. Anderson^{3e}.

8 Greene, Shattuck and Kaplowitz^{3b}. Bodansky and Jaffe⁴.

degrees of intrahepatic obstruction may contribute to the diversity of values for phosphatase activity obtained in hepatitis by different investigators

In view of the interest attaching to the subject, not only with respect to the differential diagnosis but also as regards the mechanism of jaundice, further investigation seems desirable. The observations recorded here were made in twenty-five cases of obstruction of the extrahepatic biliary tract in which the diagnosis was proved at operation or at autopsy, thirty-four cases of jaundice with a clinical course consistent with catarrhal jaundice, thirteen cases of hepatitis due to some known toxic agent, sixteen cases of cirrhosis, proved at autopsy or operation, twenty cases of neoplasm with proved involvement of the liver, and fifteen cases of miscellaneous hepatic disorders.

The results of the determination of the inorganic phosphorus and calcium contents of the serum in these cases are also recorded. The significance of variations from the normal encountered in some cases is considered briefly.

METHODS

Twenty cubic centimeters of venous blood obtained from the patient before breakfast was transferred to a 25 cc centrifuge tube, allowed to clot for one-half hour and then centrifugated at 1,000 revolutions per minute. Phosphatase activity was determined in duplicate on 1 cc. of serum by Bodansky's⁹ method. The results are expressed in Bodansky units, 1 unit being the equivalent of 1 mg of phosphorus as phosphate ion liberated from a substrate of sodium betaglycerophosphate following incubation for one hour at 37 C at a pH of 8.6. When the phosphatase activity exceeded 40 Bodansky units per hundred cubic centimeters of serum, the following positive correction was applied to the result in order to compensate for the inhibiting effect of hydrolytic products following hydrolysis of 10 per cent or more of the substrate.¹⁰

$$E_1 = E + \frac{E^2}{1,000}$$

E represents the original value expressed in Bodansky units and E_1 the corrected value in Bodansky units

The inorganic phosphorus content of the serum was determined in duplicate on 1 cc samples by the method of Kuttner and Lichtenstein,¹¹ with correction for deviations from Beer's law.¹² The calcium content of the serum was determined

9 Bodansky, A. Phosphatase Studies. II Determination of Serum Phosphatase, Factors Influencing the Accuracy of the Determination, *J Biol Chem* **101** 93, 1933.

10 Bodansky, A., and Jaffe, H. L. Phosphatase Studies. V Serum Phosphatase as a Criterion of the Severity and Rate of Healing of Rickets, *Am J Dis Child* **48** 1268 (Dec) 1934.

11 Kuttner, T., and Lichtenstein, L. Estimation of Phosphorus. Molybdic Acid-Stannous Chloride Reagent, *J Biol Chem* **86** 671, 1930.

12 Bodansky, A. Phosphatase Studies. I Determination of Inorganic Phosphate, Beer's Law and Interfering Substances in the Kuttner-Lichtenstein Method, *J Biol Chem* **99** 197, 1932.

in duplicate on 2 cc samples by the Clark and Collip¹³ modification of the Kramer and Tisdall method. The bilirubin content of the serum was estimated by the method of Thannhauser and Andersen¹⁴. The protein content of the serum was determined by difference on 1 cc samples, the macro-Kjeldahl technic being used for estimating the total nitrogen content, and Folin's method with nesslerization for determining the nonprotein nitrogen content. Albumin and globulin fractions were estimated in duplicate on 0.5 cc samples by Howe's method, nitrogen being determined by the micro-Kjeldahl technic and titration.

These methods give the following range of variation in our hands. In twenty-five normal adults the phosphatase activity of the serum varied from 1.3 to 3.5 Bodansky units per hundred cubic centimeters, in agreement with the normal range established by Bodansky (1 to 4 units). We have occasionally encountered values slightly in excess of 4 Bodansky units in patients hospitalized for a variety of diseases but without obvious disease of bone or liver. As such slight increases are exceptional and of equivocal significance, we accept 1 to 4 Bodansky units per hundred cubic centimeters as the normal range. Our experience is not in accord with that of Greene, Shattuck and Kaplowitz,^{3b} who considered values varying between 2 and 11 Bodansky units per hundred cubic centimeters of serum as without pathologic significance. In children and growing adolescents the phosphatase activity of the serum may be as high as 12 Bodansky units per hundred cubic centimeters.

Normal values for serum calcium range from 9 to 11 mg per hundred cubic centimeters, and normal values for the inorganic phosphorus of the serum, as determined by the Kuttner and Lichtenstein method, range from 2.5 to 4 mg per hundred cubic centimeters.

RESULTS AND COMMENTS

Obstruction of the Extrahepatic Biliary Tract—The phosphatase activity of the serum was found to be definitely increased in all our twenty-five cases of jaundice due to obstruction of the extrahepatic biliary tract (table 1). Preoperative values obtained in twenty-three cases ranged from 37.6 to 12.4 Bodansky units per hundred cubic centimeters. Values of less than 10 Bodansky units per hundred cubic centimeters were obtained in two cases of stone in the common bile duct in which the phosphatase activity of the serum was determined when jaundice was subsiding spontaneously. In case 25 (phosphatase, 4.6 Bodansky units) the patient was not jaundiced when the determination was made, though a stone was found subsequently at operation. In

13 Clark, E. P., and Collip, J. B. A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, *J. Biol. Chem.* **63** 461, 1925.

14 Thannhauser, J. S., and Andersen, E. Methodik der quantitativen Bilirubinbestimmung im menschlichen Serum. Ueber die Ehrlich-Proscher'sche Reaktion, *Deutsches Arch. f. klin. Med.* **137** 179, 1921.

TABLE 1—Summary of Analyses of the Blood in Twenty-Five Cases of Jaundice Due to Obstruction of the Extrahepatic Biliary Tract *

Case No	Patient	Sex	Age, Years	Cause of Obstruction	Approximate Duration of Jaundice Before Initial Blood Analysis	Uro bilin in Stool	Serum				Non protein Nitro gen, Mg per 100 Cc	Time of Blood Analysis Relative to Operation
							Phos Bodansky Units per 100 Cc	Inorganic Phos, Mg per 100 Cc	Cal-cium, Mg per 100 Cc	Bili rubin, Mg per 100 Cc		
1	J H	♂	49	Carcinoma of gallbladder	10 days	+	37.6	2.5	9.2	12.5	38	3 days before exploration
2	M J	♀	56	Carcinoma of common bile duct	3 weeks	0	35.9	2.6	9.9	19.2	27	2 days before cholecystostomy
3	M D	♂		Carcinoma of gallbladder			62.1	3.1		13.4	26	12 days after operation
4	P A	♂	45	Carcinoma of head of pancreas	3 months	0	28.6	2.6		11.4	32	(Autopsy)
							27.3	3.9		7.9	24	2 weeks before exploration
							22.8	2.6		6.5		1 day before exploration
5	J G	♂	48	Carcinoma of head of pancreas	Many weeks	0	21.4	4.9		28	29	3 days after exploration
							26.8	2.7		9.4		6 days before cholecystogastrostomy
							28.9	2.9		8.2		2 days after operation
6	A P	♀	50	Stenosis of common bile duct	5 weeks	+	8.7	2.9	7.8	2.0	22	13 days after operation
				Recurrence	23 days	+	25.2	2.9		10.7	23	3 months later
7	L W	♀	42	Carcinoma of body of pancreas	1 day	+	34.9	3.0	10.2	7.2	27	22 days after exploration †
							23.7	3.1	9.6	6.0	28	31 days after exploration
							24.2	3.0		6.3		41 days after exploration
8	R C	♀	54	Stone in common duct	3 weeks	0	34.4	3.1	8.8	9.3	30	8 days before choledochostomy
9	G R	♀	41	Carcinoma of head of pancreas	11 weeks	+	21.6	3.3	10.9	4.2	24	3 weeks before exploration
							21.1	3.1		11.7	36	2 weeks before exploration
10	E W	♂	54	Stenosis of cholecystogastros	7 days	+	23.0	3.0		10.2	40	6 months after cholecystogastrostomy
				tomy †			20.2	1.7	8.6	5.5	52	12 days later
11	D R	♂	63	Carcinoma of head of pancreas	14 days	0	15.9	4.0	7.5	3.0	24	1 day before cholecystostomy
							19.4	2.2	9.2	10.0		11 days after operation
12	L R	♂	46	Carcinoma of common bile duct	6 weeks	0	10.6	2.2	9.1	7.1	34	3 days before choledochostomy
13	K S	♀	34	Stone in common duct		+	19.3	2.8	9.5	17.0	37	1 day before choledochostomy
14	M S	♀	73	Carcinoma of gallbladder			19.0	3.6	9.6	8.5	26	(Autopsy)
15	J G	♂	40	Carcinoma of common bile duct	4 weeks	0	18.6	2.1	8.7	10.5	28	Exploration
16	J H	♂	56	Carcinoma of head of pancreas	3 weeks	+	18.3	3.2	10.1	5.4	21	1 day before cholecystoduodenostomy
17	R W	♀	50	Stone in common duct	5 days	+	17.4	3.8	10.4	3.0	31	1 day before choledochostomy
							14.7	3.4		1.0	25	12 days after operation
18	R M	♂	58	Carcinoma of papilla of Vater	8 weeks	0	10.3	3.8	9.3	14.2	27	6 days before cholecystogastrostomy
19	J P	♂	48	Stone in common duct		+	14.6	3.0	10.4	7.5	30	10 days after operation
20	M R	♀	49	Carcinoma of common bile duct, biliary fistula	1 month	+	7.3	2.5	8.1	13.7	29	4 days before choledochostomy
							13.8	3.2	10.2	4.5	26	20 days before exploration
21	M J	♂	49	Carcinoma of papilla of Vater †	3 months	0	11.0	1.6	8.1		34	8 days before cholecystogastrostomy
							13.6	4.0	10.6	10.9		1 day before operation
							16.8	3.6		14.1		12 days after operation
							9.4	3.8		6.0		27 days after operation
							8.5	3.5		4.0		10 months after operation
22	J K	♂	64	Cholangitis	5 days	+	21.2	3.0	9.8	3.4	32	8 days before cholecystogastrostomy
				Carcinoma of head of pancreas	Several weeks	0	12.6	2.7	9.7	10.0	23	1 day before operation
							15.4	3.6	9.0	10.7	33	13 days after operation
							24.7	2.1	7.4	15.0	33	27 days after operation
23	P K	♂	41	Carcinoma of head of pancreas		+	26.6	2.7	8.2	5.8	22	1 day before cholecystostomy
							12.4	4.7		2.0	26	8 days after operation
							8.7	2.3	8.0	3.0	42	45 days before autopsy
24	E M	♂	73	Stone in the common bile duct	3 weeks	+	22.7	4.8	9.7	7.5	39	5 weeks before autopsy
							6.7	1.3	9.0	2.3	25	5 days before choledochostomy
25	O O	♂	51	Stone in the common bile duct	2 weeks	+	4.6	2.9	10.0	1.0	25	

* The diagnosis was established at operation or at autopsy in every instance

† Jaundice developed twenty one days after exploration for carcinoma of the body of the pancreas

‡ Cholecystogastrostomy was performed at the time of resection of a carcinoma of the common bile duct

case 24 (phosphatase, 67 Bodansky units) jaundice was intermittent. No stones were found in the common bile duct at operation but some were present at death following recurrence of jaundice.

The values for the bilirubin content of the serum varied widely, from 19.2 to 1 mg per hundred cubic centimeters. No relation could be made out between the level of the phosphatase activity and the bilirubin content of the serum. The values for the phosphatase activity were not consistently higher in eight cases of complete biliary obstruction than in the remaining cases in which there was incomplete obstruction at the time of examination. There appeared to be no relation between the increase in the phosphatase activity of the serum and the duration of jaundice, so far as this could be ascertained. The highest phosphatase values in this series, however, occurred in cases of carcinoma obstructing the biliary tract, a group in which obstruction is likely to be of long duration and complete. But the claim that obstruction due to carcinoma can be differentiated in this manner from obstruction due to stone^{3c} could not be substantiated.

As pointed out by Roberts,² the phosphatase content of the blood in obstructive jaundice tends to be relatively high with respect to the bilirubin content of the serum. In our cases the ratio

$$\frac{\text{Serum phosphatase activity (Bodansky units per hundred cubic centimeters)}}{\text{Serum bilirubin (mg per hundred cubic centimeters)}}$$

was found to exceed 10 in all but one instance.

Although no general proportionality obtained between the phosphatase and the bilirubin level of the serum, in six of eight cases studied after the biliary obstruction was relieved surgically the resulting fall in the bilirubin content was associated with a similar but more gradual decline in the phosphatase activity of the serum.

Catarrhal Jaundice, Toxic Hepatitis—In contrast with the relatively uniform increase in values for the phosphatase activity of the serum obtained in jaundice due to obstruction of the extrahepatic biliary tract, our forty-seven cases of jaundice due to hepatitis (tables 2 and 3) yielded more variable results. In thirty-five instances the phosphatase content of the serum was less than 10 Bodansky units per hundred cubic centimeters. Of the remaining twelve cases of jaundice due to hepatitis, in which values as high as 45 Bodansky units per hundred cubic centimeters were exhibited, it is interesting to note that in six there was a history of exposure to some known toxic agent (toxic hepatitis). And in four of the remaining five cases of catarrhal jaundice analysis of the clinical history revealed complications to which the increased phosphatase content might, in part, be ascribed. In cases 29 and 34 (the patients were 12 and 14 years of age, respectively) the values obtained were within the normal limits for the age groups. One patient (case 27) had had a previous

TABLE 2—*Summary of Analyses of Blood in Thirty-Four Cases of Jaundice with a Clinical Course Consistent with That of Catarrhal Jaundice or Hepatitis of Unknown Etiology*

Case No	Patient	Sex	Age, Years	Approximate Duration of Jaundice		Uro bilin in Stool	Serum				Non protein Nitrogen Mg per 100 Cc
				Before Blood Analysis, Days	Total Duration, Days		Phos phatase, Bodansky Units per 100 Cc	Inorganic Phos phorus, Mg per 100 Cc	Calcium, Mg per 100 Cc	Bili rubin, Mg per 100 Cc	
26	B M	♀	46	4	35	0	25.3	1.9	7.9	17.7	33
				6		+	24.4	1.6	6.9	11.7	
				16		+	18.5	2.1	9.2	3.0	
				27		+	7.8	2.0	9.4	2.0	
				35		+	3.3	3.5	9.7	Trace	
				100		+	2.4	2.8	10.2	0	
27	D S	♂	42	16	5 wks	+	16.7	1.5	9.8	11.7	21
				31		+	7.1	4.1	11.0	3.0	
28	E O	♂	52	70	3 mos	+	12.9	3.4		6.0	26
				74		+	9.2	5.0	10.9	6.0	
				96		+	6.8	3.6		2.5	
29	J S	♀	12	3	13	0	11.0	4.7		8.5	
30	J C	♂	22	37	50	+	9.8	3.8		6.0	29
31	G S	♂	38	3	5	+	9.1	3.1	10.5	2.0	35
				97		+	5.6	3.1	10.1	2.0	25
32	J L	♀	52	9	43	+	9.1	2.3	9.8	20.5	23
				14		+	7.5	3.2		18.5	25
33	V	♀	25	2	14	+	8.9	3.0	10.0	8.4	27
34	S C	♀	14	16	42	+	8.9	4.3	10.6	10.5	30
				24		+	7.2	5.5	11.1	6.1	33
				36		+	11.9	5.4	10.9	7.5	35
35	E L	♂	24	14	4 wks	+	7.7	3.2	10.6	6.3	32
36	A K	♂	15	1	2 wks	0	7.2	3.0	9.7	7.2	34
37	R L	♂	23	3	3 wks	+	6.9	2.8	10.3	6.3	30
38	J G	♀	70	14	2 mos	+	6.0	2.7	10.3	14.4	25
				19		+	10.0	3.0		11.2	
				26		+	7.7	3.3		6.0	
				32		+	6.5	3.3	9.2	3.2	
				48		+	4.6	3.0		2.5	
						+					
39	A R	♀	29	15	7 wks	+	6.7	3.4	10.6	12.5	24
				32		+	8.7	3.3		7.8	
				42		+	9.4	3.5	10.6	7.7	
40	M M	♂	27	12	19	+	6.7	4.3	9.6	4.5	27
41	D O	♂	59	7	22	+	6.7	2.8	8.8	7.4	31
42	A M	♀	23	19	45	+	6.6	3.7		9.0	25
43	F M	♂	6	34	43	+	6.4	4.3		1.0	
44	J T	♀	23	15	1 mo	+	6.3	2.9		7.3	
45	E K	♀	43	5	12	+	6.3	2.8	9.8	5.0	30
				7		+	5.9	2.6		4.3	
46	M J	♀	47	8	24	+	5.9	4.0	9.6	18.0	26
47	W B	♂	39	15	25	+	5.5	2.9	11.1	10.7	29
48	K J	♂	38	15	16	+	5.4	3.5	9.9	2.0	
49	D G	♂	23	7	20	+	5.3	4.0	10.6	5.0	29
50	V G	♀	56	12	21	+	5.2	4.2		7.5	28
				19		+	3.8	4.2		3.3	
51	P N	♂	42	19	31	+	4.6	2.9	9.7	6.7	28
52	F C	♂	22	16	30	+	4.5	3.0	11.1	6.3	27
53	C C	♀	34	35	43	+	4.1	3.6	10.2	3.8	24
54	D M	♀	38	15	6 wks	+	4.0	2.9	10.0	10.4	25
55	E F	♂	40	17	36	+	4.0	2.1	10.2	3.4	28
56	M R	♂	22	26	1 mo +	+	3.9	4.0		8.5	26
57	C W	♂	37	13	28	0	3.9	3.4	9.5	8.7	50
				24		+	2.5	4.6	9.6	Trace	
58	A M	♀	49	11	21	+	3.7	2.6	10.5	4.9	23
59	M H	♂	56	17	2 mos	+	2.9	3.8		3.9	33

TABLE 3—Summary of Analyses of the Blood in Thirteen Cases of Toxic Hepatitis Following Exposure to Known Toxic Agents

Case No	Patient	Sex	Age, Years	Cause of Jaundice	Approximate Duration of Jaundice		Urobilin in Stool	Serum				
					Before Blood Analysis	Total Duration		Phos phatase, Bodansky Units per 100 Cc	Inorganic phosphorus, Mg per 100 Cc	Calcium, Mg per 100 Cc	Bili rubin, Mg per 100 Cc	Non protein Nitrogen, Mg per 100 Cc
60	A S	♀	22	Arsenical therapy	15 days 18 days 24 days	1 mo	++ ++ ++	45.0 37.9 43.7	3.8 4.4 4.2	8.9	7.5 6.9 4.8	22 22 22
61	R S	♂	37	Arsenical therapy	6 days 11 days 30 days	35 days	0 ++ ++	24.6 17.1 10.4	2.7 2.9 3.8	10.7	8.3 8.3 3.0	30 27 27
62	V B	♀	33	Arsenical therapy	17 days	2 mos	0	15.8	3.0	10.3	11.0	25
63	N O	♂	27	Arsenical therapy	20 days 31 days	9 wks	0 +	12.1 6.8	2.7 3.6	10.2	11.5 10.0	25
64	O F	♂	38	Cinchophen	9 days	27 days	+	12.1	3.7	9.5	8.3	30
65	E T	♂	2½	Phosphorus poisoning*	3 days	5 days	+	10.7	0.25	7.1	7.0	
66	M A	♂	47	Arsenical therapy	1 mo	6 wks	+	8.6	2.9	9.2	6.7	35
67	P A	♂	23	Arsenical therapy	16 days	4 wks	+	7.2	4.2	10.4	8.3	30
68	A L	♀	54	Neocinchophen	20 days	34 days	+	7.0	4.7		4.0	27
69	D R	♂	40	Arsenical therapy	5 wks 6 wks	9 wks	0 0	6.8 6.4	2.0 3.6	9.5	13.4 8.0	25
70	O A	♀	16	Third degree burn*	5 days	6 days	+	5.8	1.2	9.7	31.0	32
71	O W	♀	23	Arsenical therapy	25 days 33 days	43 days	++ ++	4.9 4.2	3.2 2.9	10.0 10.5	15.3 12.1	26
72	D K	♂	33	Arsenical therapy	6 days	9 days	+	4.0	2.8	9.6	4.4	33

* The patient died of acute yellow atrophy of the liver several days later All the other patients recovered

attack of jaundice six months before and may have had preexistent hepatic damage (see the discussion of the cases of cirrhosis) Another case (case 38) illustrates occasional transient rises in phosphatase activity of the serum during recovery from severe hepatitis

No relationship between the severity of the jaundice and the height of the phosphatase content of the serum was found in catarrhal jaundice or toxic hepatitis The ratio of the phosphatase to the bilirubin content of the serum was extremely variable, and even in the presence of intense jaundice and acholic stools there was usually little rise in the phosphatase activity There was no relation between the phosphatase level of the serum and the duration of jaundice The phosphatase activity returned to normal as the jaundice subsided

One of the difficulties encountered in the collection of cases of hepatitis arose from the fact that the exclusion of cases of stone in the common duct, with spontaneous passage, is not always possible This may be the explanation for some of the high values for phosphatase recorded in cases in which a diagnosis of hepatitis was made With this possibility in mind, all our patients were followed until the complete disappearance of jaundice, and in many instances roentgenographic examination of the abdomen and examination of the duodenal contents for cholesterol crystals were carried out We have included only those cases in which no indication of the presence of gallstones was noted

Our results support the view¹⁵ that the phosphatase activity of the serum in catarrhal jaundice and hepatitis (apart from hepatitis due to toxic drugs) tends to be only moderately increased, marked elevations being exceptions to the rule It appears that the behavior of the serum phosphatase in catarrhal jaundice or hepatitis usually differs from that in mechanical obstructive jaundice due to stone or carcinoma It is difficult to reconcile this finding with the view that jaundice in hepatitis is primarily the result of obstruction, whether intrahepatic or due to the presence of a mucous plug in the common duct¹⁶

15 Herbert^{2d} Anderson^{3c}

16 It is the opinion of most investigators that the phosphatase of the serum is elaborated chiefly in the bones, from which it escapes into the blood, whence it passes into the liver and is excreted in the bile That the bile is rich in phosphatase has been demonstrated repeatedly (Roberts,² Armstrong, King and Harris,^{3a} Greene, Shattuck and Kaplowitz^{3b}) Urine does not contain significant amounts of that phosphatase with which we are concerned here, either in normal (Roberts² and Armstrong, King and Harris^{3a}) or in jaundiced subjects (Roberts² and unpublished data)

The marked increase in serum phosphatase activity regularly observed with obstruction of the excretory channels (bile ducts) is therefore readily explained by the resulting accumulation of phosphatase in the blood The moderate increase

Of interest also is the relatively high incidence of distinctly elevated values for phosphatase in cases of jaundice which developed after the administration of arsenicals (toxic hepatitis, table 3), as compared with the values in cases of hepatitis of unknown origin

The presence of chronic hepatic damage preceding the acute attack of jaundice was suspected in some of the patients with hepatitis due to known toxic agents. When preexisting cirrhosis is present, the behavior of the serum phosphatase during an attack of hepatitis may be modified

Cirrhosis of the Liver—The phosphatase activity of the serum varied over a wide range in our sixteen cases of cirrhosis of the liver from 66.7 to 2 Bodansky units per hundred cubic centimeters (table 4). In six cases, the values exceeded 10 Bodansky units per hundred cubic centimeters. No correlation could be made out between the level of phosphatase activity and other changes which occur in cirrhosis. Marked elevations were obtained both in the presence and in the absence of jaundice, and, conversely, in one case (case 84) there was a moderate degree of jaundice without any increase in the phosphatase activity. Nor did a marked elevation appear to be more characteristic of cases of advanced cirrhosis with evidences of portal decompensation.

Autopsy or biopsy of the liver showed Laennec's cirrhosis in all but four cases in this group (case 73, biliary cirrhosis, case 80, healed subacute yellow atrophy of the liver, case 86, hemachromatosis, case 87, schistosomiasis). The inevitably heterogeneous composition of any group of cases of cirrhosis introduces so many variables that the significance of these variations in the phosphatase activity of the serum remains obscure.

Neoplastic Involvement of the Liver—The phosphatase activity of the serum was increased in seventeen of twenty cases of neoplasm with proved involvement of the liver, the values ranging from 35.2 to 43 Bodansky units per hundred cubic centimeters (table 5). In most instances in which jaundice had not developed, the phosphatase content of the serum was lower than in cases of jaundice, being within normal limits in two cases and only slightly elevated in several others. However, the phosphatase activity may be considerably elevated in cases of

in serum phosphatase activity observed in most cases of hepatitis and the marked elevation in some might well be due to the operation of a partially obstructing factor.¹⁵ But if obstruction is the cause of jaundice in hepatitis, it is difficult to understand why high values (comparable to those found with gross obstruction of the common duct) are not obtained more consistently, particularly in cases of marked bilirubinemia. The subject is discussed more fully elsewhere (Roberts,² Armstrong, King and Harris,^{3a} Herbert,^{3d} and Anderson^{3e})

TABLE 4—Summary of Analyses of the Blood in Sixteen Cases of Cirrhosis of the Liver

Case No	Patient	Sex	Age, Years	Basis for Diagnosis	Approval of Duration	Uro bilin	Date	Serum							Comment	
								Phos phatase, Bodansky Units per 100 Cc	Inor ganic Phos- phorus, Mg per 100 Cc	Cal- cium, Mg per 100 Cc	Bili rubin, Mg per 100 Cc	Non protein Nitro- gen, Mg per 100 Cc	Total Pro- tein, Gm per 100 Cc	Albu- min, Gm per 100 Cc		Glob- ulin, Gm per 100 Cc
73	E S	♀	65	Autopsy		+	3/20/36 5/7/36 6/23/36 1/4/37	66.7 51.6 15.6 31.8	1.7 1.6 1.9 1.5	9.4 8.5 8.4 8.3	6.8 5.0 5.4 5.4	29 24 30 26	7.0 6.1 5.9 6.4	3.3 2.7 2.9	2.8 3.2 3.5	Enlargement of liver, ascites, stone in cystic duct, biliary cirrhosis
74	A B	♀	43	Autopsy	Not jaundiced	+	1/2/34 1/22/34 1/30/34 6/6/35 11/6/35 4/17/36	25.1 22.5 18.1 30.3 20.3 21.9	1.6 5.2 4.0 3.4 3.1 3.0	9.7 9.3 8.8 9.2 9.0	0 0 0 Trace 2.0	32 22 29 26 27	7.9 7.9 8.4 5.3	2.1 2.4 2.3	5.5 6.0 3.0	Enlargement of liver, ascites and hydrothorax, splenectomy in 1928
75	M O	♀	33	Autopsy	Not jaundiced	+	11/19/36	15.1	3.3	9.0	0	22	5.3	2.3	3.0	Hepatosplenomegaly, pancreatitis
76	O M	♀	61	Biopsy of liver	5 months	+	10/28/35 1/25/37	13.1 10.8	2.7 3.7	9.4 7.7	2.0 5.0	32 60	7.3 5.7	1.7	4.0	Hepatosplenomegaly with ascites
77	M S	♀	53	Autopsy	2 months	+	9/22/36 10/6/36 10/20/36	11.4 12.0 19.4	2.4 2.6 3.0	8.5 8.1 10.1	2.6 3.0 4.8	22 29 30	6.0 5.1 6.6	2.0 1.9 2.0	4.0 3.5 4.6	Hepatosplenomegaly, ascites, syphilis
78	A G	♂	53	Biopsy of liver		+	11/18/35 12/10/35	10.8 21.4	3.1 4.1	10.1 9.7	4.8 5.8	30 33	7.6	3.2	4.4	Enlargement of liver, not of spleen, no ascites
79	L R	♂	44	Autopsy	3 weeks	+	7/7/36 7/9/36	6.9 3.8	2.8 0.7	9.7 9.6	7.8 8.8	36 29	7.4 7.1	1.8 1.7	3.6 5.4	Enlargement of the liver, purpura
80	J D	♂	97	Autopsy	10 weeks	0	5/15/36 6/19/36	5.2 6.9	3.3 2.6	9.3 8.6	8.2 11.2	26 23	7.2 7.2	2.2 1.7	5.0 5.5	Hepatosplenomegaly, ascites, healed subacute atrophy of liver
81	J D	♂	46	Biopsy of liver	3 weeks	+	1/30/36	6.2	3.2	9.8	4.5	32	7.6	3.2	4.4	Hepatosplenomegaly, no ascites, omentopexy 5 years before, when ascites was present
82	M J	♂	40	Autopsy	8 weeks	0	10/23/31	5.9	1.8		9.1	27	5.7	3.1	2.6	Enlargement of liver, not of spleen, ascites
83	J H	♂	51	Biopsy of liver	Not jaundiced	+	12/19/33	1.4	5.6	8.4	Trace	71	5.3	2.8	2.5	Hepatosplenomegaly with ascites
84	E M	♀	37	Autopsy		+	6/14/35 6/26/35	3.8 1.4	1.9 2.8	7.9 8.3	9.2 5.4	24 22	4.1			No enlargement of liver or spleen, no ascites
85	M F	♂	47	Biopsy of liver	Not jaundiced	+	1/6/36	3.8	1.4	8.7	1.0	37	6.1	3.2	2.9	Hepatosplenomegaly with ascites
86	J G	♂	43	Biopsy of skin	Not jaundiced	+	11/25/35	3.7	3.9	9.4	0	23	6.3	3.5	2.8	Hemachromatosis with enlarged liver, diabetes mellitus, no ascites
87	A E	♂	31	Biopsy of liver	Not jaundiced	+	1/30/36	3.6	2.7	9.9	1.0	33	5.7			Hepatosplenomegaly, no ascites, schistosomiasis
88	A Z	♂	58	Biopsy of liver	Not jaundiced	+	12/29/33	2.0	2.5	8.6	0	36	5.7	3.7	2.0	Hepatosplenomegaly with ascites

TABLE 5—Summary of Analyses of the Blood in Twenty Cases of Neoplasm with Involvement of the Liver *

Case No	Patient	Sex	Age, Years	Primary Tumor	Duration of Jaundice	Serum				
						Phos phatase, Bodansky Units per 100 Cc	Inorganic Phos, Mg per 100 Cc	Calcium, Mg per 100 Cc	Bilirubin, Mg per 100 Cc	Non protein Nitrogen, Mg per 100 Cc
89	J J	♂	52	Carcinoma of tail of pancreas	1 week	35.2	3.8	10.6	4.7	31
90	N S	♂	55	Carcinoma of body of pancreas (common bile duct patent)	13 days	24.2	2.3	10.0	6.8	13
					14 days	23.7	1.9		7.5	
					19 days	32.7	2.8		12.5	67
					21 days	26.8	4.0	9.1	11.0	
91	A R	♂	32	Carcinoma of sigmoid flexure	Several months	20.4	2.7	10.1	2.0	31
92	W M	♂	42	Carcinoma of urinary bladder	Not jaundiced	20.1	4.2	9.5	0	57
					Not jaundiced	17.7	3.2	9.1	0	45
					Not jaundiced	16.5	3.8	8.6	0	60
93	J D	♂	66	Not known	3 weeks	18.1	3.2	10.8	13.6	
94	D K	♂	56	Carcinoma of urinary bladder	Not jaundiced	15.8	4.8	9.8	0	62
95	T P	♂	41	Carcinoma of rectum		15.5	2.9		3.5	
96	M D	♀	63	Carcinoma of colon	Not jaundiced	13.8	3.0		0	30
97	M D	♂	55	Carcinoma of body of pancreas, common bile duct patent		13.7	2.9		5.7	34
98	A C	♂	52	Primary hemangiosarcoma of liver		9.7	2.3	10.0	2.0	27
99	G M	♂	35	Primary carcinoma of liver, portal cirrhosis	2 weeks later	4.6	5.4	8.5	2.0	101
					2 weeks	9.2	2.8	9.2	8.0	22
100	Y L	♀	49	Carcinoma of rectum	3 weeks	8.8	5.4	8.9	12.0	37
101	R M	♀	47	Carcinoma of body of pancreas (common bile duct patent)	Not jaundiced	6.5	2.7			
						6.1	4.2	9.4	0	30
102	N A	♀	52	Carcinoma of rectum	Not jaundiced	5.9	3.8	9.4	0	25
103	M R	♀	75	Carcinoma of gallbladder	Not jaundiced	5.6	3.2	9.6	0	25
104	R N	♀	33	Carcinoma of rectum	Not jaundiced	5.3	4.6	9.8	0	33
105	E T	♀	58	Fibrosarcoma of lymph glands	Not jaundiced	4.3	2.5	9.1	0	26
106	W G	♂	48	Carcinoma of rectum	Not jaundiced	4.0	2.7	9.4	0	20
107	K D	♀	40	Carcinoma of rectum	Not jaundiced	3.9	3.8	10.5	0	24
108	M G	♀	80	Lymphosarcoma of lymph glands	1 month	3.4	3.1	8.7	5.8	37

* Hepatic metastases were demonstrated at exploratory operation or at autopsy in every instance

hepatic metastases without jaundice, as pointed out elsewhere¹⁷ Values of more than 15 Bodansky units per hundred cubic centimeters were obtained in two cases in which there was no jaundice (cases 92 and 94) included in this series

An increase in the phosphatase activity of the serum may occur in carcinoma with skeletal metastases, particularly of the osteoplastic type,¹⁸ and this possibility must be borne in mind when one is considering the significance of phosphatase values in cases of neoplasm In case 92 osteoplastic metastases were present in the spine, ribs and pelvis, and the rise in the phosphatase activity in this case cannot be ascribed solely to the metastases in the liver In case 94 roentgenographic examination of the skeleton failed to reveal metastases to the bones An increase in the phosphatase activity was observed in several other cases of carcinoma (not included here) with enlargement and irregularity of the liver, in which exploratory operation or autopsy was not performed

The fact that in several cases of neoplasm an increase in the phosphatase activity of the serum was the only indication of hepatic metastases—there being no bilirubinemia or clinically obvious hepatic enlargement—led to the hope that the determination might prove useful in the early detection of metastases Our results suggest that increased values for serum phosphatase occur with more regularity than increased values for serum bilirubin in such cases, but, as table 5 shows, the value for phosphatase may be normal or only equivocally increased in the presence of definite involvement of the liver

Miscellaneous Cases—The data for three cases of hemolytic jaundice (cases 109 to 111) are included in table 6 The phosphatase activity of the serum was within normal limits, a result in accord with previous findings¹⁹ Of exceptional interest are the results obtained for two infants with jaundice due to atresia of the biliary tract Contrary to expectations, the phosphatase content of the serum was within the normal limits of variation for the age group, despite the obstructive character of the jaundice The phosphatase activity was definitely ele-

17 Gutman, A B, Swenson, P C, and Parsons, W B The Differential Diagnosis of Hyperparathyroidism, *J A M A* **103** 87 (July 14) 1934

18 (a) Gutman, A B, and Gutman, E B Paget's Disease Relative Constancy of Serum Phosphatase Levels Over Periods up to Two Years, *Proc Soc Exper Biol & Med* **33** 150, 1935 (b) Gutman, A B, Tyson, T L, and Gutman, E B Serum Calcium, Inorganic Phosphorus and Phosphatase Activity in Hyperparathyroidism, Paget's Disease, Multiple Myeloma and Neoplastic Disease of the Bones, *Arch Int Med* **57** 379 (Feb) 1936 (c) Woodward, H Q, Twombly, G H, and Coley, B L A Study of the Serum Phosphatase in Bone Disease, *J Clin Investigation* **15** 193, 1936

19 Roberts² Greene, Shattuck and Kaplowitz^{3b} Herbert^{3d} Anderson^{3e}

TABLE 6—Summary of Analyses of the Blood in Fifteen Miscellaneous Cases

Case No	Patient	Sex	Age	Diagnosis	Duration of Jaundice	Uro bilin in Stool	Serum					Comment
							Phos phatase, Bodansky Units per 100 Cc	Inorganic Phos phorus, Mg per 100 Cc	Cal cium, Mg per 100 Cc	Billi rubin, Mg per 100 Cc	Non protein Nitrogen, Mg per 100 Cc	
109	B G	♂	9 days	Hemolytic jaundice	9 days	+	9.6	10.6	9.5	10.3	30	
110	B G	♂	21	Congenital hemolytic jaundice	Many years	+	2.2	3.3	9.5	4.0	48	
111	L F	♂	12	Congenital hemolytic jaundice	Many years	+	1.7	2.5	10.3	3.0	37	
112	A D	♂	2 mos	Congenital atresia of bile ducts	7½ weeks	0	11.1	3.2	11.0	10.4	21	Proved at operation
113	I G	♂	1 mo	Congenital atresia of bile ducts	3 weeks	0	6.3	3.7	10.1	12.7	23	Proved at autopsy
114	N O	♂	33	Amebic abscess of liver		+	11.8	3.6		0	70	Clinical diagnosis
115	S S	♂	22	Gaucher's disease of liver and spleen		+	3.1	3.9	10.3	0	29	Proved at operation, biopsy
116	T S	♂	74	Hepatitis, Paget's disease	6 days	+	32.0	2.3	8.9	8.0	25	2 days later Amylase in blood, 18 units
117	J B	♂	57	Hepatitis (?), stone in common duct (?), acute pancreatitis		+	28.5	2.5		2.5		6 days later, 60 units of amylase
						+	4.1	1.3		9.4		8 days later, 90 units of amylase
						+	10.1	2.9		2.9		9 days later, 120 units of amylase
						+	25.2	3.0		2.3		12 days later, 30 units of amylase
						+	19.2	3.3		1.5		35 days later, 21 units of amylase
						+	10.7	3.0		Trace		
						+	2.7	3.4				
118	J M	♂	45	Suppurative cholangitis, carcinoma of hepatic duct, multiple abscesses of liver	4 weeks	+	8.2	2.8		19.0	29	2 weeks later
						+	5.9	3.4		11.0		
119	J K	♂	25	Cholecystitis and cholelithiasis, acute pancreatitis	4 days	+	5.5	1.8	9.2	4.3	35	1 day before cholecystostomy
							5.5	3.3	9.4	1.0	30	7 days postoperatively
							4.3	3.8	10.3	Trace	33	14 days postoperatively
120	F B	♀	28	Cholecystitis	4 days	0	7.3	2.9	9.6	7.5	27	1 day before cholecystostomy
							7.1	3.3	9.1	2.0	36	5 days postoperatively
							8.7	3.8	10.3	2.0	30	16 days postoperatively
							10.4	3.8	9.2	8.8	82	1 day after cholecystostomy
121	A W	♂	52	Cholecystitis and cholelithiasis	2 days		6.9	1.9	8.2	9.4	67	3 days postoperatively
							9.7	2.5	8.7	4.0	43	10 days postoperatively
							6.5	3.0	8.7	2.0	28	19 days postoperatively
							5.8	1.9	8.2	Trace	29	34 days postoperatively
							15.6	3.6		5.2	29	4 days before cholecystostomy
122	D S	♂	38	Cholecystitis	6 days	0						
123	M O	♀	75	Cholecystitis and cholelithiasis	3 days	+	14.3	1.9	10.2	8.8	27	1 day before cholecystostomy

vated in one case of amebiasis of the liver without jaundice. It seems probable that this elevation was the result of intrahepatic disease. One patient with Gaucher's disease of the liver and spleen (case 115) proved to have normal phosphatase activity. Case 116 further illustrates the necessity for exclusion of certain diseases of bone in the interpretation of values for serum phosphatase for jaundiced patients. In this instance an unexpectedly high value in a case of hepatitis was shown by roentgenograms to be due to the presence of Paget's disease, unsuspected until then. In case 117 jaundice of unknown etiology was complicated by an attack of acute pancreatitis, evidenced by the clinical symptomatology and by a sharp rise in the amylase content of the blood. There was a concomitant transient increase in the phosphatase activity of the serum, whether due to partial obstruction of the common bile duct or of the pancreatic duct could not be determined. In case 118 the condition could not be classified satisfactorily because of uncertainty as to the degree of obstruction caused by a carcinoma of an intrahepatic bile duct at the hilus of the liver.

In the remaining five cases in this group there was a clinical suggestion of obstructive jaundice due to calculi in the common bile duct. Exploratory operation failed to confirm this diagnosis, however, though in all cases there were evidences of cholecystitis and in some cases there was also cholelithiasis (table 6). In these instances the possibility that calculi were present in the common bile duct and became dislodged shortly before operation could not be excluded. The clinical picture could be explained as plausibly, however, by transitory edema of the common bile duct or head of the pancreas or by acute hepatitis complicating inflammation of the gallbladder.

Results of the Determination of the Inorganic Phosphorus and Calcium Contents of the Serum—The inorganic phosphorus content of the serum was within normal limits in most of the one hundred and twenty-three cases included in this study. In a number of instances, however, the values for inorganic phosphorus were less than the lower limit of normal variation.²⁰ Hyperphosphatemia was observed in several cases. A satisfactory analysis of the factors affecting the inorganic phosphorus content of the serum in these cases was not possible, but from the data at hand certain inferences regarding the general mechanism involved seem permissible.

20 Although many patients with jaundice were on a diet high in carbohydrate and low in fat, ingestion of dextrose, which causes a fall in the value for serum phosphorus (Harrop, G. A., Jr., and Benedict, E. M. The Participation of Inorganic Substances in Carbohydrate Metabolism, *J Biol Chem* **59** 683, 1924), need not be considered as a cause of the hypophosphatemia, as the results recorded here were obtained during fasting.

It was noted that the incidence of hypophosphatemia was highest in cases of cachexia with wasting due to cirrhosis of the liver (table 4)²¹ or to carcinoma obstructing the common bile duct (table 1). In a significant proportion of these cases hypophosphatemia was associated with hypocalcemia and was thought to be due to prolonged malnutrition. Impairment of hepatic function may contribute to the fall in the inorganic phosphorus content of the serum, since the incidence of hypophosphatemia in these cases is considerably greater than that observed in cases of carcinoma in general.²² The marked hypophosphatemia noted in two cases of acute yellow atrophy is further suggestive of this view. In one of these cases (case 65) the inorganic phosphorus content of the serum was by far the lowest in our experience—0.25 mg per hundred cubic centimeters.

Hyperphosphatemia was associated with definite retention of nitrogen in several cases, and it was ascribed to impairment of renal function. Two patients (cases 29 and 34, table 2) with values over 4 mg per hundred cubic centimeters were adolescent children, and the results may be regarded as within normal limits.

The calcium content of the serum was within normal limits in most of our cases of hepatitis (tables 2 and 3) and of carcinoma with metastases to the liver (table 5) and in our miscellaneous cases of jaundice (table 6). Moderate hypocalcemia was noted in nine of fifteen cases of cirrhosis of the liver (table 4) and in eight of eighteen cases of carcinoma obstructing the common bile duct (table 1). On analysis of the clinical and chemical findings in the latter groups it became apparent that a number of factors must be considered in any attempt to analyze the mechanisms involved in the development of hypocalcemia in diseases affecting the liver.

Gunther and Greenberg²³ have called attention to the significance of a decreased value for serum albumin in this connection, since a fall in the amount of calcium bound to protein is reflected in the values

21 Labbe and Fabrykant (*Le phosphore*, Paris, Masson & Cie, 1933) have called attention to lowered values for total phosphorus of the blood in cirrhosis of the liver and have pointed out that the inorganic phosphorus fraction may be decreased. They obtained normal values for a small group of patients with catarrhal jaundice. Fiessinger and Boyer³¹ obtained similar results. Our data do not justify the conclusion³¹ that these two conditions may be differentiated by determining the inorganic phosphorus content of the serum.

22 Jackson, H., Jr., and Taylor, F. H. L. Calcium, Potassium and Inorganic Phosphate Content of the Serum in Cancer Patients, *Am J Cancer* **19** 379, 1933. Gutman, Tyson and Gutman^{18b}.

23 Gunther, L., and Greenberg, D. M. The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, *Arch Int Med* **45** 983 (June) 1930, The Diffusible Calcium and the Proteins of the Blood Serum in Malignant Diseases, *ibid* **46** 67 (July) 1930.

for total serum calcium. The serum proteins were partitioned in eight of our cases of cirrhosis of the liver associated with hypocalcemia. The albumin content of the serum was found to be decreased in every instance, the highest value obtained in this group being 37 per cent (table 4). In case 83, however, the fall in the value for serum calcium might be ascribed to hyperphosphatemia and retention of nitrogen.

Hypocalcemia was not present in some cases of cirrhosis of the liver, despite definite decreases in the albumin content of the serum. In several such cases considerable elevation in the value for serum globulin was found, and the maintenance of the level of serum calcium within normal limits might have been effected by an increase in calcium bound to globulin. In view of the prevailing uncertainty as to how much,²⁴ if any,²⁵ calcium is bound by serum globulin, particularly in pathologic states, the validity of this explanation remains in doubt. Even large increases in the content of serum globulin did not suffice in some instances to maintain the content of serum calcium within normal limits when the value for serum albumin was markedly decreased.

In many of our cases of cirrhosis of the liver the patient was in an advanced stage of cachexia, so that, in addition to hypoproteinemia due to malnutrition, the effect on the value for serum calcium of protracted deprivation of calcium might be considered. In cases of obstruction of the common bile duct due to carcinoma (table 1) this is an important consideration, since the absorption of calcium is affected adversely by the absence of bile from the gastro-intestinal tract. A further complication was introduced in some cases in this group by the presence of a biliary fistula, either spontaneous (case 20) or operative. As shown experimentally in dogs with biliary fistula,²⁶ loss of calcium in the bile may result in hypocalcemia. In some of our patients an attempt to avoid the diversion of bile from the body was made by means of cholecystogastrostomy, but the effect of this procedure on the content of serum calcium was not always apparent.

Values for serum calcium of less than 9 mg per hundred cubic centimeters were obtained in only four of our forty-seven cases of

24 Schmidt, C. L. A., and Greenberg, D. M. Occurrence, Transport and Regulation of Calcium, Magnesium and Phosphorus in the Animal Organism, *Physiol Rev* **15** 297, 1935. Weir, E. G., and Hastings, A. B. The Ionization Constants of Calcium Proteinate Determined by the Solubility of Calcium Carbonate, *J Biol Chem* **114** 397, 1936.

25 Bendien, W. M., and Snapper, I. Untersuchungen über die Bindung der Kolloide des Serums mit Hilfe von Ultrafiltern erhöhter Durchlässigkeit, *Biochem Ztschr* **260** 105, 1933.

26 Cavazza, F. Su di alcune ricerche biochemiche nel sangue, nella bile e nel fegato di animali con fistola biliare permanente, *Pathologica* **27** 241, 1935.

hepatitis The value for serum calcium was as low as 6.9 mg per hundred cubic centimeters in one instance (case 26) in which the value for serum protein at the time was 5.7 per cent No protein partition was carried out The calcium level of the serum may fall below normal limits in cachectic patients with carcinoma (table 5), as has long been known ²⁷

SUMMARY AND CONCLUSIONS

The phosphatase activity, inorganic phosphorus and calcium of the serum were determined in the following cases: twenty-five cases of obstruction of the extrahepatic biliary tract in which the diagnosis was proved at operation or at autopsy, thirty-four cases of jaundice with a clinical course consistent with catarrhal jaundice, thirteen cases of toxic hepatitis due to some known toxic agent, sixteen cases of cirrhosis of the liver, proved either at autopsy or at operation, twenty cases of neoplasm with proved involvement of the liver, and fifteen miscellaneous cases

The phosphatase activity of the serum was increased in every case of jaundice due to obstruction of the common bile duct, the values exceeding 10 Bodansky units per hundred cubic centimeters in twenty-three of twenty-five instances The phosphatase activity of the serum was elevated irrespective of the degree or duration of jaundice and whether obstruction was complete or incomplete

The phosphatase activity of the serum was found to be more variable in catarrhal jaundice or hepatitis, but values of less than 10 Bodansky units per hundred cubic centimeters were obtained in thirty-five of forty-seven cases The incidence of marked elevation in phosphatase activity was much higher in cases of hepatitis due to known toxic agents than in cases of catarrhal jaundice or hepatitis of unknown cause Our results support the view that the phosphatase activity of the serum in catarrhal jaundice and hepatitis (apart from hepatitis due to toxic drugs) tends to be only moderately increased, a marked elevation being an exception to the rule

As values for phosphatase activity which are not definitely elevated tend to rule out jaundice due to obstruction of the common bile duct, the method is useful in the differential diagnosis of jaundice

The phosphatase activity of the serum varied over a wide range in cirrhosis of the liver No correlation could be made out with the degree or duration of jaundice or with the stage of the disease

²⁷ Gutman, Tyson and Gutman^{18b} Jackson and Taylor²² General reviews of the literature on the serum calcium in jaundice are available (Snell, A. M., and Greene, C. H. The Calcium of the Serum in Jaundice, *Am J Physiol* **92** 630, 1930 Gray, J. S., and Ivy, A. C. The Role of Serum-Calcium Fractions in the Effect of Viosterol on the Bleeding Tendency in Jaundice, *Am J Digest Dis & Nutrition* **2** 368, 1935)

The phosphatase activity of the serum exceeded the normal limit of variation in most cases of carcinoma with metastases to the liver. The rise in the phosphatase activity is usually definite before the development of jaundice. Since skeletal metastases, particularly of the osteoplastic type, often cause an increase in the phosphatase activity of the serum, their presence must be ruled out.

The phosphatase activity of the serum was within normal limits for the age group in two infants with jaundice due to atresia of the biliary tract. This finding was unexpected, since the jaundice in these cases was of the obstructive type.

The phosphatase activity of the serum was within normal limits in three cases of hemolytic jaundice.

The inorganic phosphorus and calcium contents of the serum were within normal limits in most cases in this series. Hypophosphatemia and hypocalcemia occurred in a significant proportion of these cases, most frequently in cachectic patients with cirrhosis of the liver or with carcinoma obstructing the common bile duct, and also in two cases of acute yellow atrophy. Hypocalcemia in patients with cirrhosis of the liver was usually associated with a decrease in the albumin content of the serum.

CARBOHYDRATE METABOLISM IN EPILEPSY

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In the widespread search for a possible relation between bodily disease and epilepsy, carbohydrate metabolism has been studied by numerous authors. The occurrence of convulsions in states of hypoglycemia either as a result of the injection of insulin or spontaneously in the course of hyperinsulinism has further focused attention on the possible disorders of this function.

One of the difficulties encountered in such a study lies in the absence of indications of dysfunction not primarily related to diabetes. Examinations of large numbers of normal subjects have been made more with the view of determining the character of metabolism not related to diabetes than of evaluating the functions of the organs concerned in carbohydrate metabolism. Therefore, what are described as normal types of curves, with arbitrarily constructed formulas, may be applicable for subjects who are not diabetic or destined to be diabetic, but they do not give any indication of what is occurring when high curves, flat curves or delayed curves are obtained for subjects not prediabetic or diabetic. Yet all these types of curves are designated as normal. Another difficulty is found in the constantly changing standards and in the differences of technic. Much further work is necessary on the function of normal organs under varying conditions before one may do more than compare the results obtained in a group of patients suffering from epilepsy with a group not so afflicted, both being examined under approximately the same conditions.

There has been no uniformity of opinion as to the effect of the type of diet preceding the dextrose tolerance test. Some authors, Sweeney,¹ for example, have stated that no effect is produced on the general curve by a variation of diet. Others, for instance McClellan

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1 Sweeney, J S. A Comparison of the Effects of General Diets and of Standardized Diets on Tolerance for Dextrose, *Arch Int Med* **42** 872 (Dec) 1928

and Wardlow,² have said that high blood sugar levels are present in patients who received a diet restricted as to carbohydrates before the test, and Kohn, Fries and Felshin³ found a higher rise and a delayed fall when ketosis had been induced by diet. In most instances dextrose tolerance is determined after oral ingestion. Myers and McKean,⁴ among others, have called attention to the effect of variability of time of gastric emptying and of intestinal absorption on the character of the curve for dextrose after oral ingestion. As a consequence, McKean, Myers and Von der Heide⁵ have devised a "micro-interval glucose tolerance test," employing intravenous administration.

Others, notably Lennox and Bellinger,⁶ have said that there is a close correspondence between the curves obtained after intravenous and those after oral administration. The amount of dextrose administered has varied with different investigators, some using a fixed amount (100 Gm, irrespective of the subject's weight), others, an arbitrary amount (1.75 Gm per kilogram of body weight), and still others, a fixed larger amount (up to 250 Gm). Thus, John⁷ used a standard amount of 100 Gm. He found a variation in the type of curve for those who were obese and for those who were undernourished. Svensgaard⁸ found that in the case of children when 250 Gm was used, the curves obtained were somewhat higher and more prolonged.

Variation in the technic likewise accounts for some divergence of opinion. Although in many instances the Folin-Wu tungstic acid method is basic, it is known that this is not absolutely accurate, and a true indication of the dextrose tolerance can be obtained only if a method such as that of Somogyi is used. The latter eliminates the nonsugar reducing substances, the readings usually being 15 or 20 mg per hundred cubic centimeters lower, as demonstrated by Holt and Greisheimer.⁹

2 McClellan, N. S., and Wardlow, H. S. H. Hypoglycemic Reactions Following Glucose Ingestion, *J Clin Investigation* **11** 513, 1932.

3 Kohn, J. L., Fries, M. E., and Felshin, Gertrude. Spontaneous and Induced Ketosis in Children, *Am J Dis Child* **34** 857 (Nov.) 1927.

4 Myers, G. B., and McKean, R. M. The Oral Glucose Tolerance Test, *Am J Clin Path* **5** 299, 1935.

5 McKean, R. M., Myers, G. B., and Von der Heide, E. C. Blood Glucose Clearance, *Am J M Sc* **189**:702, 1935.

6 Lennox, W. G., and Bellinger, Margaret. Blood Sugar. Comparison of Blood Sugar Curves Following Ingestion and Intravenous Injection of Glucose, *Arch Int Med* **40** 182 (Aug.) 1927.

7 John, H. J. A Study of Eleven Hundred Glucose Tolerance Tests, *M J & Rec* **131** 287, 351 and 398, 1930.

8 Svensgaard, Elizabeth. Blood Sugar in Normal and Sick Children, *Acta pædiat* (supp 4) **12** 1, 1931.

9 Holt, G. W., and Greisheimer, E. M. "True" Glucose Tolerance in Forty-Two Normal Individuals, *Proc Soc Exper Biol & Med* **28** 547, 1931.

and Campbell, Osgood and Haskins,¹⁰ who showed by a combination of yeast and the tungstic acid method an 11 to 32 mg lower reading in the former

There is also a difference in the amount of dextrose present in venous and in capillary blood, Myers and McKean⁴ have shown in venous blood that the high peak is usually below 170 mg per hundred cubic centimeters and that it falls to the level for fasting in two hours, whereas in capillary blood the peak is below 200 mg per hundred cubic centimeters and falls below 120 mg in two and one-half hours

Measurements of the amount of dextrose in the blood after its administration have been made at varying intervals, usually during fasting and one-half, one, two and three hours after the administration. It seems that in the future an additional estimation should be made at the fourth hour. Since most of the investigations have been made in relation to the diagnosis of diabetes, the curves usually have been divided into those for diabetic and those for nondiabetic patients. They are variously described. Mosenthal¹¹ classified the curves as normal when the rise was between 120 and 160 mg, high when the rise was a peak of 160 mg, prolonged when the curve failed to drop below 120 mg at the end of the second hour, high prolonged when the curve rose above 160 mg and failed to return to 120 mg at the end of the second hour and low when the curve did not rise above 120 mg. John⁷ classified the curves into straight (with little or no rise), normal (with a rise to between 160 and 200 mg but a return to the fasting level in one and one-half hours), prediabetic (with a delay in the return to the fasting level in two and one-half or three and one-half hours) and diabetic (when the return to the fasting level was delayed for from three and one-half to six hours). The consensus is that a normal curve starts at less than 120 mg at the fasting level, rises to a peak not over 160 mg and returns in less than two hours to the fasting level. In children it has been found that the return to the fasting level may be delayed for a longer period, two and one-half or three hours. It has been pointed out that overweight children have a lower tolerance for sugar.

The significance, if any, of the variability of the curves in apparently normal subjects is unknown. John found that among 287 subjects of normal weight there were 25.8 per cent with diabetic curves, according to his definition. Therefore, the report of high levels in such conditions

10 Campbell, R. A., Osgood, E. E., and Haskins, H. D. Normal Renal Threshold for Dextrose, *Arch Int Med* 50:952 (Dec) 1932.

11 Mosenthal, H. O. The Interpretation of Sugar Tolerance Tests. The Common Occurrence of Renal Glycosuria, *M Clin North America* 9:549, 1925.

as dementia praecox (Lorenz¹²) will not be significant until the precise meaning of the term high is understood. High prolonged curves likewise have been found in many diversified conditions of ill health—hyperthyroidism, nephritis, thrombo-angitis obliterans, carcinoma, epithelioma (Mosenthal), hepatic disease (Gray¹³), acromegaly, melancholia, Parkinson's disease, etc (Myers and McKean). Large series of these individual conditions must be studied so that when values are found that are higher than those for a large series of normal subjects, the significance may be determined. In this connection it seems that a failure of hepatic homeostasis is responsible for high prolonged curves in experimental animals (Soskin and Mirsky¹⁴).

Coller and Troost¹⁵ have stated that in hepatic damage the fasting level for sugar is low and the dextrose tolerance curve tends to be of a diabetic type. To the failure of hepatic homeostasis Soskin and Mirsky¹⁴ also attributed the occurrence of hypoglycemic reactions following the ingestion of dextrose. McClellan and Wardlaw² have described this hypoglycemic reaction as occurring in many conditions—fasting, exhaustion, low renal threshold for dextrose, endocrine and hepatic disease, infections and other miscellaneous disorders. They have noted its tendency when there is only a small rise after the administration of dextrose.

Not only is there a variability of the type of curves in any large material, but individual curves obtained on different occasions show a wide variation in a group of normal subjects, similarly, in those suffering from epilepsy. Lennox¹⁶ found that the 20 per cent of high curves obtained at one time was reduced to 10 per cent at a succeeding time. The degree of variability of curves in successive examinations in a group of normal subjects must be further studied.

THE FASTING LEVEL IN EPILEPSY

Wide variations are noted in the amount of sugar in the blood conceived to be within normal limits. This of course is in part due to the methods of examination, the type of diet received preceding the test, the state of general health and other factors perhaps not compara-

12 Lorenz, W. F. Sugar Tolerance in Dementia Praecox and Other Mental Disorders, *Arch Neurol & Psychiat* **8** 184 (Aug.) 1922.

13 Gray, Horace. Blood Sugar Standards, *Arch Int Med* **31** 241 and 259 (Feb.) 1923.

14 Soskin, Samuel, and Mirsky, I. A. The Influence of Progressive Toxic Liver Damage upon the Dextrose Tolerance Curve, *Am J Physiol* **112** 649, 1935.

15 Coller, F. A., and Troost, F. L. Glucose Tolerance and Hepatic Damage, *Ann Surg* **90** 781, 1929.

16 Lennox, W. G. Studies of Metabolism in Epilepsy, *Arch Neurol & Psychiat* **18** 395 (Sept.) 1927.

ble for all the groups reported on. The consensus is that the uppermost level is 120 mg per hundred cubic centimeters. Concerning the lowest normal level there is no agreement. Lennox, O'Connor and Bellinger¹⁷ have placed it at 80 mg, Nielsen,¹⁸ at 75 mg, and Tyson, Otis and Joyce,¹⁹ at 80 mg.

Although an average of 100 mg per hundred cubic centimeters may be the normal lower level, marked variations occur in supposedly normal subjects to levels below 75 mg. The numbers of such variations in a group must be further determined before any significance can be given to the occurrence of a small percentage of readings below 80 mg and above a certain minimum.

Lennox, O'Connor and Bellinger, reviewing the literature prior to 1927, showed that an examination of the fasting level for dextrose in the hands of many investigators, usually in a small number of cases, reveals a wide variance of conclusions. Some have called attention to hyperglycemia (Heidema) and some to hypoglycemia (Wladyczko and Josephs). Others found normal values (Kooy, Westen, Holmstrom, Shaw and Moriarty). Of two authors with a large material, Wuth in 40 patients found a range from 60 to 118 mg, with an average of 90 mg. Weeks, Reimer, Allen and Wishard in 45 patients found values between 46 and 125 mg. Lennox, O'Connor and Bellinger¹⁷ in 2,000 examinations of 267 patients found extremes of 63 and 232 mg, the great majority being between 80 and 120 mg. Fifteen per cent were beyond normal limits, 4 per cent being above 120 mg and 11 per cent below 80 mg. They concluded that the study failed to show any abnormality in the concentration of sugar in the blood in epilepsy. Felsen²⁰ in 50 patients found 8 with a sugar content of less than 75 mg and 6 with a value over 120 mg per hundred cubic centimeters. Munch-Petersen and Schou²¹ in 166 patients found the following fasting levels: 60 to 69 mg in 5 per cent, 70 to 79 mg in 26 per cent, 80 to 89 mg in 45 per cent, 90 to 99 mg in 22 per cent and 100 mg in 1 per cent. They used the Hagedorn-Jensen method of examination and did not consider these values as significant.

17 Lennox, W. G., O'Connor, Marie, and Bellinger, Margaret. Studies of Metabolism in Epilepsy. II. The Sugar Content of the Blood, *Arch Neurol & Psychiat* **18** 383 (Sept.) 1927.

18 Nielsen, J. M. Convulsions of Undetermined Etiology. Studies of the Blood Sugar, *Arch Neurol & Psychiat* **31** 1055 (May) 1934.

19 Tyson, G. N., Jr., Otis, L., and Joyce, T. F. Study of Blood Sugar of Epileptics, *Am J M Sc* **190** 164, 1935.

20 Felsen, Joseph. Laboratory Studies in Epilepsy, *Arch Int Med* **46** 180 (Aug.) 1930.

21 Munch-Petersen, C. J., and Schou, H. I. Investigations into the Sugar-Metabolism in Epileptics, Especially the Sugar Threshold in Adrenalin- and Glucosis-Hyperglycemia, *Acta psychiat et neurol* **6** 545, 1931.

Nielsen¹⁸ in 58 cases of epilepsy noted a periodic or constant tendency to show a low sugar content, considering the low figure to be 10 per cent below that of normal persons, and he said he thought that a tendency to hypoglycemia is present in about 90 per cent of patients with epilepsy

Tyson, Otis and Joyce¹⁹ reported that in 56.4 per cent of 92 patients the fasting level was below 80 mg. Haury and Hirschfelder²² quoted Pigott as stating in a communication before the American Psychiatric Association on May 14, 1935, that a low fasting level for sugar is found in epileptic patients. They examined 25 patients before, during and after seizures and in each case found normal limits before the seizure, in no instance finding hypoglycemia.

In our own material studies in carbohydrate metabolism were carried out on a group of 55 males, ranging in age from 9 to 58 years and in 35 females from 13 to 45 years of age (tables 1 and 2). In 42 males and in 29 females repeated fasting levels were available because both dextrose and insulin tolerance tests were made. The studies were generally made from one to five days apart.

The Randles and Grigg²³ micromethod was used in making the determinations. This procedure is like the usual Folin-Wu method, but only 0.1 cc. of blood is employed. It was carried out on capillary blood obtained from the finger. This method, according to Foster,²⁴ gives higher and sharper curves for carbohydrate tolerance than does venous blood taken simultaneously. The fact that arterial blood was used is of some value in interpreting the dextrose tolerance curves.

Among the males the fasting level for sugar was found to vary from 52 to 125 mg. per hundred cubic centimeters of blood. The average level was 78.54 mg. and the median 78 mg. In the female patients the levels varied from 55.5 to 102.5 mg., with an average of 79.5 mg. and a median of 80.5 mg. The average level for the entire group was therefore 78.5 mg. and the median 78.8 mg. This is well within the normal range for fasting levels. One must keep in mind that such a figure must be considered as flexible for any given subject, despite the group constancy, provided the subject's level remains within physiologic limits. The reason is seen when an attempt is made to correlate the fasting level on two occasions. Here there is noted a coefficient of correlation

22 Haury, V. G., and Hirschfelder, A. D. Some Observations upon Blood Glucose in Epilepsy, *Proc. Soc. Exper. Biol. & Med.* **32** 1658, 1935.

23 Randles, F. S., and Grigg, W. K. Estimation of Blood Sugar by the Folin-Wu Method, Using One Tenth Cubic Centimeter of Blood, *J. A. M. A.* **82** 684 (March 1) 1924.

24 Foster, G. L. Carbohydrate Metabolism, *J. Biol. Chem.* **55** 291 and 303, 1923.

(1) of 0.27 (Pearson product-moment method) So low a correlation indicates that it is impossible to predict a second reading from a first, even within a day or so, with the patient under constant conditions. This, of course, may explain why different workers have reported

TABLE 1—*Dextrose Tolerance Tests—Males*

Patient	Age	Weight, Pounds	Dose of Dex- trose*	Sugar, Mg per 100 Cc of Blood					Comment
				Fasting	½ Hour	1 Hour	2 Hours	3 Hours	
20	9	75.50	+	67.0	104.0	181.0	81.2	125.0	Glycosuria
82	9	63.75		86.2	136.0	194.0	94.0	92.0	Glycosuria
80	14	85.00		64.4	90.2	64.4	82.5	47.2	
42	14	105.00		75.7	97.5	84.0	62.9	77.5	
1	14			75.5	135.0	79.0	90.0	78.0	
72	15	148.00		83.0	124.0	136.0	121.0	75.8	
45	16	160.00		78.8	68.5	79.5	61.0	64.5	
6	16	125.00		75.5	124.0	102.0	90.0	79.0	
27	17	101.50	+	69.0	136.0	156.0	75.6	79.0	
86	18	150.00		113.0	150.3	169.4	141.0	95.0	
75	18	138.75	+	93.0	112.0	160.0	90.0	79.0	
A	18	116.00		73.5	110.0	142.0	45.6	81.0	
85	19	132.00		79.3	112.0	88.8	100.0	80.0	
5	20	119.75	+	91.5	125.0	102.0	74.0	80.0	
9	20	147.75		62.5	109.0	97.0	92.5	101.0	
32	22	138.00		72.0	100.0	103.0	64.0	52.1	
2	23	149.00			106.0	117.0	71.0	74.0	
6	23	131.00	+	74.5	109.0	83.3	70.9	70.2	
3	24	116.00		71.0	159.0	141.0	113.0	98.0	
30	24	128.50		79.0	119.0	141.0	111.0	72.0	
15	24	139.00		79.0	159.0	153.0	90.0	65.5	
60	25	132.00	+	65.5	108.5	84.0	66.5	111.4	
46	26	146.00	+	95.0	143.0	172.5	115.0	84.0	Glycosuria
88	26	167.00		84.3	128.0	95.2	89.7	60.0	
39	27	128.00		80.5	112.0	129.0	101.0	95.5	Glycosuria
63	27	121.00	+	76.0	127.0	161.0	115.0	95.0	
74	28	156.00		66.0	100.5	99.0	55.0	53.9	
83	29	167.00		100.0	143.9	137.0	66.4	65.7	
65	29	118.25	+	79.0	162.0	160.0	103.0	95.0	
51	29	135.50	+	64.0		111.5	107.0	26.0	
84	31	141.75		100.0	122.0		165.0	133.0	
17	32	135.00		88.0	140.0	117.0	139.0	57.0	
24	34	106.00	+	86.0	139.0	160.0	82.0	102.0	
64	35	168.25		85.0	161.0	143.0	85.0	71.0	
40	35	210.00	+	81.0	102.0	86.0	74.0	75.0	
73	36	165.00	+	83.0	106.8	148.5	56.0	89.5	
71	37	177.00		61.0	140.0	108.0	80.5	66.3	
61	38	156.00		69.2	134.0	146.0	134.0	90.0	
78	39	114.50		78.0	102.0	153.0	95.0	79.0	
10	39	126.00		72.5	102.1	106.2	79.5	63.4	
67	39	150.75		63.0	144.0	135.0	38.0	124.0	
23	40	156.75		79.0	123.0	220.0	118.0	123.0	Glycosuria
B	41	107.25		68.5	126.0	147.0	137.0	74.4	
69	42	152.50		72.0	103.0	94.5	39.0	61.0	
66	43	126.25		52.0	102.0	105.0	72.0	44.2	
14	43	220.00	+	88.5	128.0	159.0	127.0	70.5	Glycosuria
8	46	154.25		80.6	130.0	144.0	70.3	81.5	
70	47	190.00	+	69.0	166.0	86.0	137.0	82.0	
17	50	134.00		77.5	176.0	105.3	76.5	45.5	
22	52	160.25	+	81.0	136.0	154.0	155.0	86.0	Glycosuria
57	54	131.00		59.0	81.0	86.0	58.0	42.5	
C	55	133.25		83.0	174.0	172.0	122.0	97.0	Glycosuria
25	57	128.50	+	93.0	222.0	204.0	147.0	33.0	Glycosuria
79	58	143.50		103.0	246.0	326.0	164.0	119.5	Glycosuria
D	58	125.25		98.5	187.0	139.0	33.2	71.9	Glycosuria

* The oral dose of dextrose was 1.75 Gm per kilogram of body weight except when a + sign is inserted to show that 200 Gm was given.

widely divergent readings for the fasting levels of patients suffering from epilepsy, although all the levels have fallen within physiologic limits.

It might be predicted from the lack of correlation between two fasting levels for dextrose for the same patient that any attempt to

correlate the fasting level with so constant a factor as the age or the weight would meet with failure as regards a significant r . This is apparent from our scatter diagrams. When the correlation of the fasting level for dextrose with the weight is studied, the same failure is observed, whether the patient is underweight, overweight or normal. The outcome is identical if the fasting level is compared with the quotient of the weight divided by the age, the weight being corrected for the height and age according to standard tables prepared for insur-

TABLE 2—*Dextrose Tolerance Tests—Females*

Patient	Age	Weight, Pounds	Dose of Dex- trose*	Sugar, Mg per 100 Cc of Blood					Comment
				Fasting	½ Hour	1 Hour	2 Hours	3 Hours	
37	13	118 00		72 2	89 0	82 0	72 0	87 0	
49	13	88 25	+	75 0	149 0	118 0	115 0	127 0	Glycosuria
55	14	78 00	+	89 5	252 0	295 0	193 0	156 0	Glycosuria
12	15	104 00	+	98 5	148 0	214 0	191 0	102 0	
48	16	96 75		83 5	150 0	141 0	158 0	97 0	Glycosuria
E	16	128 25		88 8	135 1	130 0	88 4	82 0	
4	16	180 00	+	83 0		148 0	78 0	114 0	
F	17	100 50		74 0	137 0	111 0	92 1	62 5	
87	17	116 00		76 0	105 0	105 0	97 0	57 0	
89	17	170 75		79 6	149 0	162 0	117 0	84 0	
90	18	115 00		78 8	122 2	128 0	82 7	50 0	
38	18	159 00			154 0	111 0	91 2	74 0	
31	19	90 00	+	72 3	136 2		147 7	31 3	
59	19	116 50	+	72 8	146 5	138 0	77 0	118 0	
49	20	92 50	+		184 0	173 0	196 0		Glycosuria
54	21	112 00		102 5	110 9	111 0	108 5	85 5	
6	24	110 25		80 0	177 0	198 0	132 0	97 0	
43	26			83 0	134 0	137 0	78 0	87 5	
29	28	126 50	+	81 0	126 0	102 0		70 0	
41	29	133 00	+	60 5	95 0		52 5	51 0	
53	30	111 50	+	84 0	147 0	118 0	114 3		Glycosuria
36	31	124 00		84 5	187 0	151 5	113 3	122 5	
61	32	213 00		75 0	211 0	236 0	138 0	105 0	Glycosuria
26	32	101 50		84 0	132 0	122 0	113 0	94 0	
56	33	129 50		73 0	93 5	101 5	103 5	85 8	
2	33	121 75		65 3	90 9	75 4	64 3	47 6	
18	34	125 25	+	83 0	160 0	139 0	96 0	107 0	
21	35	123 00		79 0	102 0	49 0	78 5	52 5	
33	37	95 00	+	84 4	86 6	105 0	71 0	56 2	
62	37	113 50	+	83 0	96 0	108 0	98 5	85 5	
42	40	128 00		97 0	176 0	147 0	132 0	104 3	Glycosuria
60	41	190 25	+	72 2	137 0	104 0	53 4	103 0	
19	42	191 25		85 1	107 0	111 0	83 5	91 0	
58	42	136 25	+	79 4	117 5	145 5	76 5	76 0	
44	45	135 75	+	75 3	136 0	141 0	77 5	68 2	

* The oral dose of dextrose was 1.75 Gm. per kilogram of body weight except when a + sign is inserted to show that 200 Gm. was given.

ance companies. There appears to be no significant correlation. A boy of 9 years might have the same fasting level as a man or woman of 40 or vice versa. The males weighed more than the females—136.4 pounds (62 Kg.) as against 120 pounds (54.5 Kg.) for the median. The males were also somewhat older, 30 to 26.3 years for the averages and 27.5 to 26 years for the medians.

Changes in the amount of dextrose in the blood have been reported as occurring in relation to epileptic seizures. Lennox, O'Connor and Bellinger¹⁷ noted the reports of a number of investigators dealing with small numbers of patients, in various instances stating that the amount

of sugar was low, high or normal before an attack, and they concluded from their study that there was no direct relation between the level for sugar and the seizures. In 3 of 11 patients whose blood was examined immediately after a seizure Felsen²⁰ found hypoglycemia. Haury and Hirschfelder²² found a rise in the sugar content during the convulsion proportional to the severity of the attack. In our studies there appeared to be no relation between the fasting level for sugar and the seizures, whether the attacks occurred before or subsequent to the drawing of blood. The fallacy of single readings (to determine a hypoglycemic level) is especially evident in this phase of the study. Thus, readings of 68 and 67.6 mg per hundred cubic centimeters might be obtained for patients just before an attack, whereas on other occasions, when no attack was imminent, the readings were 83 and 75 mg, respectively. However, wider divergences, as between 65 and 103 mg and 58 and 87 mg, for two readings were noted for patients who have had no attacks for years. There was no difference in the fasting levels in the cases of organic epilepsy as compared with those of idiopathic epilepsy.

It appears, therefore, that the fasting level in this group of 90 patients falls well within normal limits. It does not vary with age, weight, bromide medication or type of epilepsy. Low levels are seen just before attacks in some patients as frequently as they are seen in others who have not had a seizure for years.

SUGAR TOLERANCE CURVES IN EPILEPSY

Prior to the work of Lennox and Bellinger,¹⁷ only in small series of patients suffering from epilepsy were curves for sugar tolerance reported. They reported on the study of 140 patients. Considering a rise above 160 mg as high and a rise of less than 120 mg as low, they found 37 per cent high, 15 per cent low and 48 per cent normal curves. When they analyzed their material, considering a rise to over 165 mg or a failure to return to 120 mg at the second hour as high and a rise to not more than 110 mg as flat, they had 24 per cent high, 6 per cent flat and 70 per cent normal curves. Their data gave no evidence of any abnormality of carbohydrate metabolism that might in itself induce seizures. In relation to the significance of any change in carbohydrate metabolism in epilepsy, Lennox and Cobb²⁵ said that "a minority of patients show an abnormal or variable response to the administration of glucose, for which the explanation is obscure." Munch-Petersen and Schou²¹ found variable curves in their 166 patients but did not think they were significant. In 58 patients Nielsen¹⁸ found 50 who failed to show a rise above 120 mg and 15 who failed to show

25 Lennox, W. G., and Cobb, S. *Epilepsy from the Standpoint of Physiology and Treatment*, Medicine 7: 105, 1928.

a rise above 100 mg in the first half hour, 39 failed to show a return to the fasting level at the third hour and in 11 the lowest point occurred at the fourth hour. These results are at considerable variance with those reported by others. Tyson, Otis and Joyce¹⁹ in a study of 7 patients found delayed and high curves for 2 patients who had the most frequent attacks.

Dextrose was given orally, one group being given 200 Gm irrespective of weight and the others 175 per kilogram of weight. Blood was drawn from the finger after one-half, one, two and three hours. Specimens of urine were examined for evidence of glycosuria. Ninety patients were studied (tables 1 and 2), the curves being classified as high when showing over 160 mg per hundred cubic centimeters of blood and low when the acme of the curve did not reach 120 mg. Delayed curves were those that did not fall to at least 120 mg at the second hour and others that were found to be at a significant point above the fasting level at the third hour. Thus, a curve might be high delayed, i. e., over 160 mg at

TABLE 3—*Dextrose Tolerance Curves, Summary*

	High Curves		Low Curves		Normal Curves	
	Number	Percentage	Number	Percentage	Number	Percentage
Males	11	20	13	24	31	56
Females	12	35	7	18	15	47
Totals	23	26	20	21	46	53

the acme and not below 120 mg at the second hour, or it might be normal delayed. The hypoglycemic phase of the curve was studied, especially in relation to the response of the patient to the administration of insulin.

Twenty-six per cent of the dextrose tolerance curves were high, 53 per cent normal and 21 per cent low (table 3). The highest value noted was 326 and the lowest 80 mg. Statistical correlation of the type of curve to the age, weight, age and weight, sex, and blood pressure were such as to make the coefficient of no value. There was no relationship between the fasting level and the height of the curve or between the lowest level of the insulin tolerance curve and the highest level of the dextrose tolerance curve. Cognizance was taken of the fact that 41 per cent of the patients were underweight. Their weights were corrected in accordance with insurance tables, but the correlation to the highest dextrose value was only 0.218. Only 19 of the entire group were more than 5 per cent overweight, as compared with average values. Of these, only 7 (37 per cent) showed high curves, while 9 showed normal and 3 showed low curves. This is not in keeping with John's figures of 65.6 per cent high curves for obese patients. Only 12 patients were more than 10 per cent overweight, and 4 of these showed high curves.

Thirty-three patients, 17 males and 16 females, were given 200 Gm of dextrose, irrespective of their weight. Five females and 1 male showed high curves, 3 females and 2 males low curves and 8 females and 13 males normal curves. The 19 per cent high curves for patients given 200 Gm of dextrose is even lower than the 26 per cent of high curves for the entire group. Giving a patient an overdose of dextrose is in no way a factor in the production of a high curve. This is in keeping with Gray's¹³ studies of the comparative responses of patients given varying amounts of dextrose in a tolerance test.

In the age correlations attention may be called to the fact that for the males studied here the high curves were clustered in the group from 50 to 59 years old, while for the females they were in the group from 10 to 19 years old. Since only 1 of these patients had hypertension and none was obese, the reason for this apparently paradoxical distribution must be sought elsewhere. The closest correlating factor seemed to be organic epilepsy. These high curves were seen in 3 of the 7 girls who had organic epilepsy, while 4 others with organic epilepsy showed normal curves. Every high curve for patients 50 years of age or more was seen in a subject with organic epilepsy. However, the cause of the organic change was early senescence, and it is entirely possible that the same disintegrative factors were at work breaking up the hemostatic mechanism for carbohydrate metabolism and producing senescence and epilepsy. This small group of older men was the only one in the present study in which there was a definite age correlation.

As had been noted in the section on the fasting level of the blood sugar, bromide levels of from 75 to 300 mg per hundred cubic centimeters caused no alteration in the acme of the dextrose tolerance curves.

Some workers have considered curves which fail to return to a level below 120 mg at the second hour as abnormal. There were 11 patients (12.3 per cent) who showed this type of curve. Four of these showed an acme in the curve below 160 mg and a return to a normal level by the third hour. Seven were patients who showed peaks over 160 mg, and 4 showed peaks over 215 mg. All but 2 of the patients showed a drop in the curve to a normal level by the third hour, 1 showing a return to 133 mg and another with a curve reaching 295 mg showing a return to 156 mg. The latter patient, a girl of 14 years, had been having numerous epileptic attacks just before the test was made. The fasting level was 85 mg. There were no other significant correlative data in these second hour delayed curves. Eighteen patients showed a significant failure for the curve to return at the third hour (20 per cent). Nine were males and 9 females. In 9 of the 18 patients the curve failed to fall below 110 mg at the third hour, and in 6 cases it failed to fall below 120 mg. This failure to return after three hours was apparently

not related to a high peak, as in 9 patients who showed a third hour delayed curve the peak was high and in 9 it was normal

In no instance was there diabetes, hyperthyroidism or nephritis, the common causes for high or high delayed curves. Hypertension was noted in only 1 of the 18 patients

The dextrose tolerance curve for 12 females and 23 males (39 per cent of the patients) dropped below the fasting level. This was not related to the height of the curve (only 6 of the 35 showed high curves, 11 showed low curves). Four of the males had been given 200 Gm of dextrose, but 12 other males who were given the same dose had no hypoglycemic phase. Nine of the 12 females had been given 200 Gm. This might be significant were it not for the fact that 7 other females who were given 200 Gm of dextrose showed no hypoglycemic phase. The hypoglycemic phase was not related to any phase of the insulin tolerance curve, the percentage of the return or the returns above the fasting level. The hypoglycemic phase has been reported as occurring in normal persons (Gray and others). Hawk and Bergheim²⁶ have pointed out that dextrose tolerance studies of (arterial) blood from the finger show curves that are more likely to present a hypoglycemic phase.

The character of the dextrose tolerance curve is not related to the type of epilepsy, organic or functional. An analysis reveals that 39 per cent of the patients with organic epilepsy showed high curves (this of course includes the men over 50), 32 per cent low curves and 35 per cent normal curves.

Finally, the type of curve is unrelated to the result of treatment. Seventy per cent of those with high curves, 63 per cent with low curves and 77 per cent with normal curves were improved on treatment. There is not sufficient difference in the three groups to make the type of dextrose tolerance curve significant as a prognostic measure.

The dextrose tolerance curves in our study may be fractionally analyzed and summarized by comparison with similar analyses of the investigations of others who used the same technic (table 4). Our fasting levels are below those given both for normal and for epileptic subjects and are closest to the figure given by Nielsen¹⁸. Our one-half hour reading is about that given for normal subjects, except that given by Gray, which is higher and falls between the values given by Nielsen and Lennox for epilepsy. At one hour our reading is a trifle higher than the normal reading and falls between the values in epilepsy, being close to Lennox' figure. At two hours our average is below all the normal levels and again falls between the values given by Nielsen and Lennox for epilepsy. At three hours our values are below the normal levels.

26 Hawk, P. B., and Bergheim, O. *Practical Physiological Chemistry*, Philadelphia, P. Blakiston's Son & Co, 1931

and slightly above Nielsen's value for epilepsy. The values in the three groups of patients suffering from epilepsy are sufficiently close together to be considered similar. Furthermore, all the values are well within normal zones (charts 1 to 3).

Statistical study of these curves places them closer to normal than any other curves reported for nondiabetic conditions (hypertension without nephritis, renal glycosuria without nephritis, renal glycosuria with

TABLE 4—*Dextrose Tolerance Tests*

	No of Subjects	Sugar, Mg per 100 Cc of Blood			Standard Deviation	Coefficient of Variability
		Average Values	Median Values	Range		
Normal Subjects						
Gray						
Fasting	276	96.2	97.8	160-40	19.3	20.0
½ hour	158	149.8	148.1	230-60	31.2	20.8
1 hour	300	126.8	121.2	280-40	37.6	29.8
2 hours	252	111.1	109.5	260-30	30.0	27.0
3 hours	103	97.9	95.0	170-40	21.7	22.2
Lennox						
Fasting	23	102.9	98.6	141-79	14.7	14.4
½ hour	23	140.4	133.7	239-87	33.4	23.2
1 hour	23	122.2	118.3	188-56	34.2	28.0
2 hours	23	115.4	109.3	165-80	20.4	17.6
Nielsen						
Fasting		88.0				
½ hour		137.0				
1 hour		129.0				
2 hours		103.0				
3 hours		87.0				
Epileptic Patients						
Lennox						
Fasting	139	96.2	95.7	229-68	15.5	16.2
½ hour	137	145.2	145.1	500-83*	29.4	20.2
1 hour	138	136.8	127.9	318-69	42.8	31.2
2 hours	136	117.0	110.5	295-67	34.0	29.0
Nielsen						
Fasting		80.0				
½ hour		119.0				
1 hour		104.0				
2 hours		87.0				
3 hours		76.0				
Our Results						
Fasting	86	78.5	79.0	52-113	12.2	15.6
½ hour	86	133.8	128.7	68.5-252	34.6	25.0
1 hour	84	134.3	129.0	49-326	42.0	31.2
2 hours	86	97.2	92.0	33.2-196	35.0	36.0
3 hours	85	82.7	81.7	33-156	23.8	28.8

* Statistical computations in this series are based on a range between 240 and 80 mg. Three atypical values between 300 and 500 mg. were omitted in order to represent accurately the more homogeneous measures.

chronic nephritis, nondiabetic pregnancy with a high sugar level, hyperthyroidism, hypothyroidism, hepatic disease, acromegaly, or hyperpituitarism, and hypopituitarism, or dyspituitarism.)

THE RENAL THRESHOLD FOR SUGAR

Opinions about the level of the blood sugar at which sugar should appear in the urine are extremely varied. Mosenthal reported 170 mg. per hundred cubic centimeters, Campbell, Osgood and Haskins put it in a range between 125 and 220 mg., while John found that glycosuria

occurs at levels below 180 mg of dextrose in the blood in 83.8 per cent of normal subjects. He has called attention to an individual threshold for each person. In some cases no glycosuria occurred when the amount of dextrose in the blood was over 200 mg per hundred cubic centimeters. In from 16 to 20 per cent of the normal subjects in whom it occurred there was over 180 mg of dextrose per hundred cubic centimeters of blood, as well as in 20 per cent of the underweight and 46 per cent of the obese subjects.

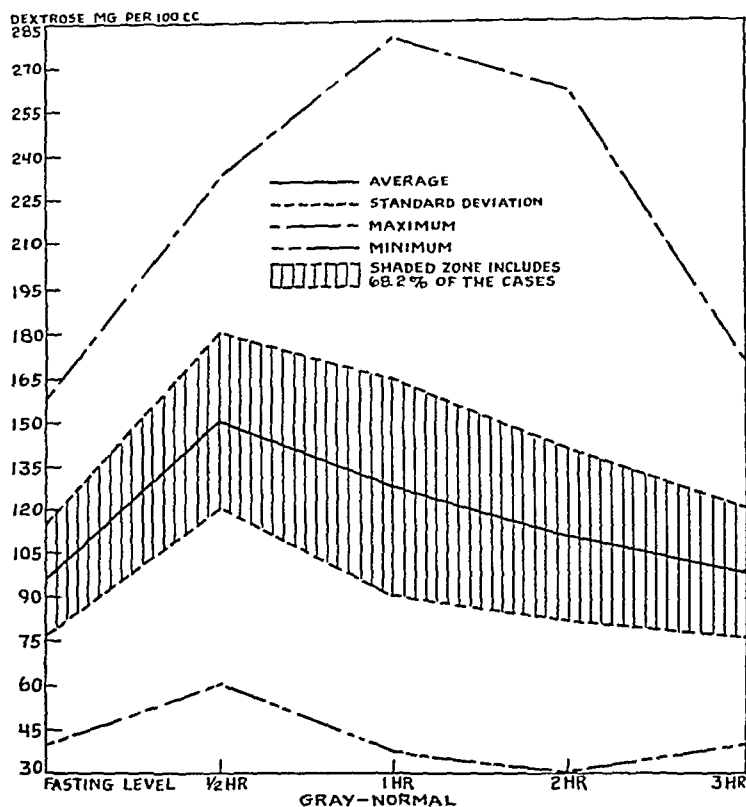


Chart 1—Dextrose tolerance curves for normal subjects reported on by Gray. The shaded zone indicates the normal values.

Lennox and Bellinger, from 209 observations on 140 patients, found glycosuria in 32 per cent. At the end of the second hour in 64 per cent there was glycosuria when the value for blood sugar was over 200 mg, in 50 per cent when it was between 175 and 199 mg, 21 per cent when it was between 150 and 174 mg, 28 per cent when it was between 125 and 149 mg and 10 per cent when it was below 125 mg. Felsen, not measuring the amount of sugar in the blood, noted that after the ingestion of 200 Gm of dextrose only 15 of 47 patients excreted sugar in the urine at the end of the second hour. He concluded from this that epileptic patients can tolerate and store large amounts of carbohydrate. Munch-Petersen and Schou in a study of 36 patients found no sugar in the urine of 9 when the blood sugar content was about 180 mg, of 7 when it was below

160 mg and of 2 when it was above 250 mg. Since they combined injections of epinephrine and of dextrose, the results are not comparable with those given in other reports.

Of 90 patients with hyperglycemia induced by the oral administration of dextrose, only 18 showed glycosuria, 11 males and 7 females (20 per cent). Most of the patients who showed urinary sugar had attained a high level of dextrose tolerance, although sugar was present in the urine of patients with levels as low as 129 mg. for blood sugar.

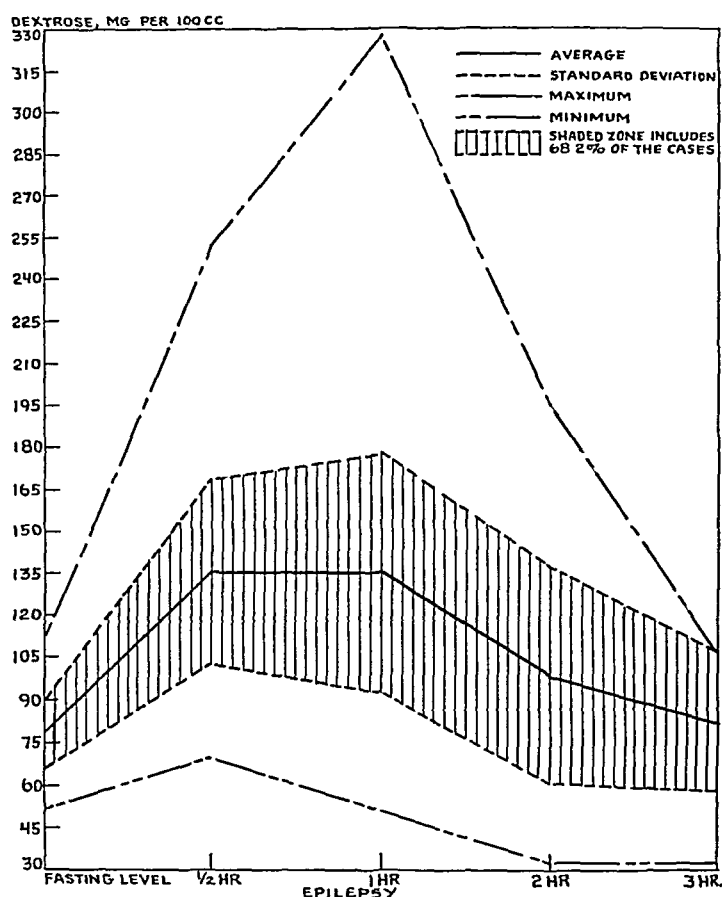


Chart 2—Dextrose tolerance curves for our series of epileptic patients

Eleven of the 18 patients showed high curves, i e., over 160 mg., and 3 did not fall below 120 mg. at the second hour (so-called diabetic type of curve). On the whole, the normal thresholds were high, 189 mg. for the females and 187 mg. for the males, an average of 188 mg. for the group. However, as has been pointed out by many authors, individual analyses do not follow group figures. Thus one sees an occasional level as high as 290 mg. unaccompanied with dextrose in the urine. The ranges given by John for normal subjects show an average of above 140 mg. and below 180 mg. observed in 83.8 per cent of the patients. Only 9 (69.2 per cent) of 13 of our patients with over 180 mg. of

sugar in the blood had glycosuria. If the normal threshold is considered as 160 to 180 mg (Hawk and Bergheim²⁶), 14 patients showed an increased tolerance. However, individual variations forbid the stressing of this point.

Of more significance is the fact that there are no evidences of a decreased tolerance, i. e., glycosuria with a low content of blood sugar, as in "renal diabetes."

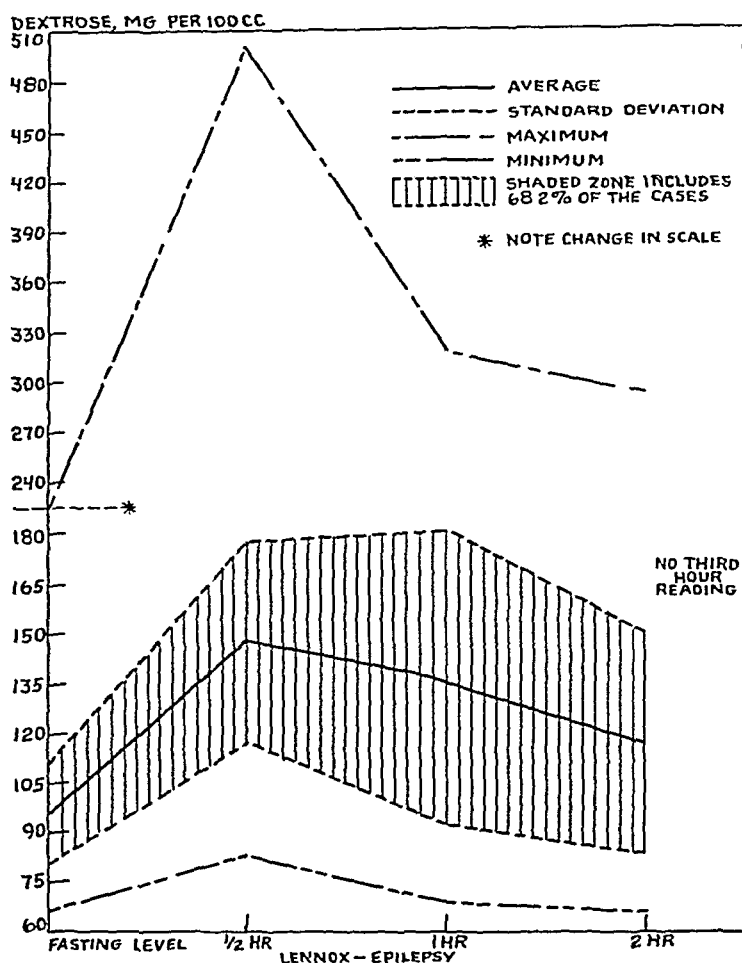


Chart 3—Dextrose tolerance curves for the epileptic patients reported on by Lennox

INSULIN TOLERANCE TESTS

Analogous to the increase of sugar in the blood after the administration of dextrose is its diminution after the injection of insulin. After the injection of insulin the amount of sugar in the blood diminishes at a certain rate, then increases at a certain rate to the fasting level. The insulin has been injected intravenously and intramuscularly. It has been given in certain stated amounts, as 10 units, irrespective of the subject's weight, and in certain amounts representing 0.1 unit per kilogram of body weight. As with tests for sugar tolerance, so with those for insulin tolerance—there seems to be a marked variability in

the response of normal subjects, and the complete significance of certain deviations is not known

McCormick, MacLeod, Noble and O'Brien²⁷ have said that the extent of the reduction of the sugar content does not follow closely the dose per kilogram or correspond to the actual level of the blood sugar before the injection is given. Neither does the method of injection, intramuscular or intravenous, make any significant change in the steepness of the curve. The subsequent behavior depends partly on the dose of insulin and partly on the glycogen content of the liver. Sevringhaus, Kirk and Heath²⁸ examined 8 students, 4 units of insulin being given to 4, 8 to 2 and 10 to 2. They found that the types of curves varied and were unrelated to the dose per kilogram of body weight. The duration likewise was variable, and the symptoms of hyperinsulinism appeared at no definite level. Roughly, the extent and duration seemed parallel to the dose.

Bodansky and Simpson²⁹ examined men after the intravenous injection of 2 units of insulin and found that the lowest level occurred about eighteen minutes after the administration. The total depression they considered as related to the weight, and the depression was slower in fat persons. The return began immediately after the lowest point was reached and was complete in seventy-five minutes, being delayed in those who were overweight. This relation to weight has been observed by others. For example, when 10 units of insulin was injected subcutaneously, it was observed that in obese persons the average fall was 28 mg, whereas in undernourished subjects it was 59 mg. Collens and Grayzell,³⁰ injecting 0.2 unit per kilogram of body weight intravenously, found the lowest sugar level at the end of the first half-hour and a rapid recovery to the fasting level within forty-five minutes. Better to study the type of curve, Sendrail³¹ computed the area enclosed by joining with the base line the points of the sugar levels during fasting, one-half hour and at other intervals, and in this way obtained an indication of the depth in fall and the slowness of the return as reflected by differences in the areas. In addition, he noted in 16 normal sub-

27 McCormick, N. A., MacLeod, J. J. R., Noble, E. C., and O'Brien, K. The Influence of the Nutritional Condition of the Animal on the Hypoglycemia Produced by Insulin, *J. Physiol.* **57** 234, 1923.

28 Sevringhaus, E. L., Kirk, Elizabeth, and Heath, H. J. The Duration and Magnitude of the Hypoglycemia After Insulin, *Am. J. M. Sc.* **166** 677, 1923.

29 Bodansky, Aaron, and Simpson, Sutherland. Blood Sugar of Normal Human Subjects After the Intravenous Injection of Insulin, *Quart. J. Exper. Physiol.* **17** 57, 1927.

30 Collens, W. S., and Grayzell, H. G. Blood Sugar Response to Intravenous Insulin in Normals and in Diabetics, *Proc. Soc. Exper. Biol. & Med.* **28** 487, 1931.

31 Sendrail, M. L'épreuve de tolerance a l'insuline, *Ann. de med.* **27** 289, 1930.

jects that the drop in the amount of sugar averaged 24 mg and that the return to the fasting level occurred within an average of sixty-five minutes and never with an interval of over ninety minutes

Although variations occur, the expected curve is one in which the greatest fall is noted within the first half-hour when the insulin is given intravenously or in large amounts subcutaneously, and probably it is the same when doses of 10 units are given subcutaneously. The return begins promptly and is complete in less than three hours, usually within thirty-five minutes, the average interval being sixty-five minutes. Increased sensitivity, reflected by a greater fall than is expected in the normal subject, has been observed in diabetic patients and in animals with an Eck fistula (Sprague³²). In animals like rats a return to a level below the original fasting level has been observed after the third hour. This may persist for as long as six hours and has been explained on the basis of inanition (Hrubetz³³).

The percentage of normal subjects in whom the fall exceeds the arbitrary figure of 30 mg per hundred cubic centimeters must be ascertained. In some instances after a standard dose of 10 units of insulin, a fall of from 9 to 45 mg has been recorded in normal subjects and as high as from 42 to 62 mg in undernourished subjects. The delay in fall, the delay in return and the failure of return also must be carefully studied in a large number of normal subjects. For the most part one can only record the findings for a group of patients with epilepsy and guess at the general resemblance to expected normal curves.

Baudouin and Azérad³⁴ examined 19 patients with epilepsy, injecting 10 units of insulin intravenously. They recorded an expected fall in the first half-hour in 16 of the patients, and all showed a return nearly to the fasting level by the third hour. In 4 the sugar content of the blood dropped below 30 mg, in 1 to 16 mg.

In an article which appeared after our study had been completed, Ziskind and Bolton³⁵ reported on insulin tolerance tests on 40 patients with epilepsy. In 20 patients trauma, syphilis, encephalitis, alcoholism, psychoneuroses, narcolepsy or an "organic condition" was thought either to be the cause of the convulsive disorder or to be associated with it. The major thesis of their experiment was to determine the effect of induced hypoglycemia on the convulsions. They gave from 10 to

32 Sprague, Randall G. Effect of "Chronic" Experimental Liver Damage on the Blood Sugar Response to Insulin, *Am J Physiol* **110** 488, 1934.

33 Hrubetz, M. Caroline. The Time Curve After Insulin, *Am J Physiol* **110** 384, 1934.

34 Baudouin, A., Azérad, E., and Lewin, J. Epreuve d'hypoglycémie insulinique chez les épileptiques, *Compt rend Soc de biol* **114** 902, 1933.

35 Ziskind, Eugene, and Bolton, Ruth. Insulin Hypoglycemia in Epilepsy, *Arch Neurol & Psychiat* **36** 331 (Aug) 1936.

60 units of insulin subcutaneously to the 40 patients, and in no instance did a convulsion ensue, although in 1 instance the sugar content of the blood dropped to 28 mg per hundred cubic centimeters

The fact that the doses of insulin, varying from 10 to 60 units, were so much greater than those used by us in all but 5 cases, precludes any comparison of the curves. However, a failure for the curve to

TABLE 5—*Insulin Tolerance Tests—Males*

Patient	Age	Weight, Pounds	Units of Insulin	Sugar, Mg per 100 Cc of Blood				
				Fasting	½ Hour	1 Hour	2 Hours	3 Hours
20	9	75.50	10	73.5	47.0	78.0	90.5	88.0
82	9	60.75	10	109.0	77.0	62.2	64.0	55.0
11	11		10	80.0		50.2	37.8	48.1
28	14	93.00	10	92.0	68.5	41.5	91.0	80.5
80	14	85.25	10	54.5	60.4	37.9	21.9	33.1
42	14	105.00	10	73.0	50.7	51.5	58.8	59.0
72	15	148.00	10	73.5	67.0	60.0	67.0	80.0
45	16	160.00	10	94.0	62.7	51.5	74.0	77.0
11	16	118.00	10	80.0	76.6	46.5	57.8	60.0
86	18	150.00	10	125.0	94.3	65.7	67.4	82.0
75	18	138.75	10	93.5	77.0	82.0	75.0	94.0
A	18	116.00	10	71.0	40.0	40.5	34.2	37.2
85	19	132.00	10	64.8	42.3	54.0	49.5	64.5
5	20	119.75	10	70.5	70.5	48.0	60.0	64.5
32	22	138.00	10	73.0	38.0	36.0	46.0	61.0
6	23	131.00	10	82.0	75.0	37.5	53.5	67.2
46	26	146.00	10	78.4	49.2	53.2	60.6	74.2
88	26	167.00	10	67.6	36.0	Too low	52.6	66.0
39	27	128.00	10	76.2	49.8	35.1	47.2	46.2
63	27	121.00	10	73.0	60.0	49.0	56.6	66.8
74	28	156.00	10	66.0	55.2	38.5	43.0	49.5
65	29	118.25	10	80.5	47.1	41.6	47.6	63.5
84	31	141.75	10	86.8	57.4	32.8	46.0	56.1
64	35	168.25	10	86.0	64.0	61.0	71.0	56.0
73	36	165.00	10	87.0	76.0	93.0	81.0	51.0
71	37	177.00	10	67.0	58.0	30.9	51.2	50.9
61	38	156.00	10	115.0	74.0	79.0	53.0	80.0
78	39	114.50	10	79.5	69.5	44.0	51.0	44.0
10	39	126.00	10	77.4	62.1	22.5	25.0	26.3
5	39	150.75	10	78.0	50.0	40.0	31.0	35.0
68	39	153.00	10	78.0	68.0	63.0	38.0	53.0
69	42	152.50	10	52.6	34.6	34.8	40.2	42.7
66	43	126.25	10	68.0	39.0	35.4	42.7	41.8
8	46	154.25	10	108.0	83.5	68.2	54.5	76.0
70	47	190.00	10	70.5	39.0	47.0	51.5	55.3
77	50	134.00	10	97.0	78.0	38.0	43.3	51.8
57	54	131.00	10	86.6	59.0	37.5	24.5	17.0
C	55	133.25	10	71.0	75.0	62.0	47.5	39.5
25	57	128.50	10	79.5	89.0	41.5	43.2	51.3
79	58	143.50	10	96.0	86.5	64.5	43.5	56.0
D	58	125.25	10	101.0	79.3	40.3	62.3	73.0

return to the fasting level at the end of the third hour was seen in 28 of the 29 patients for whom the fasting level was recorded in their table.

Insulin tolerance tests were performed on 70 of the patients with epilepsy, 41 males and 29 females who were included in our dextrose tolerance studies (tables 5 and 6). Each was given 10 units of insulin subcutaneously, regardless of the body weight, except 9 females, who were given 0.1 unit per kilogram of body weight. While the general response of these 9 females was similar to that of the rest of the group, certain differences will be worth pointing out later in the detailed description.

All but 5 of the 70 patients showed a fall within one-half hour after the administration of insulin. These 5 showed a reduction in the sugar level at the first hour, but 3 showed little or no return at three hours, 1 a poor return and 1 a fairly good return. The last patient showed the same level at one-half hour as during fasting. The other 4 showed a rise one-half hour after the administration of insulin. The curves for these 5 did not differ in depth from those for the others.

While it seems from the literature that the lowest level should be attained within one-half hour and the return to near-fasting levels within ninety minutes, our studies do not bear this out. Of the 70

TABLE 6—*Insulin Tolerance Tests—Females*

Patient	Age	Weight, Pounds	Units of Insulin	Sugar, Mg per 100 Cc of Blood				
				Fasting	½ Hour	1 Hour	2 Hours	3 Hours
37	13	118.00	5.3	84.0	32.8	68.5	83.0	72.6
55	14	78.00	10.0	85.5	63.4	40.0	52.3	64.0
12	15	104.00	10.0	73.5	68.5	35.0	22.0	29.6
48	16	96.75	4.4	69.0	72.8	59.7	63.2	66.6
L	16	128.25	10.0	66.5	54.5	33.8	39.2	52.5
4	16	130.00	10.0	87.0	57.5	49.0	65.5	94.0
F	17	100.50	4.6	90.0	37.0	43.0	36.0	52.0
87	17	116.00	10.0	74.6	66.1	31.0	46.5	55.0
89	17	170.75	10.0	77.2	61.3	56.7	45.0	48.0
90	18	115.00	10.0	84.0	76.2	76.7	50.0	54.0
38	18	159.00	7.1	89.0	43.5	50.0	72.6	81.5
31	19	90.00	10.0	75.4	45.4	30.7	44.3	62.0
59	19	116.50	10.0	96.0	65.8	57.4	57.2	56.5
49	20	92.50	10.0	77.5		51.0	58.0	57.0
54	21	112.00	5.9	72.9	29.7	42.5	69.0	78.0
G	24	110.25	10.0	91.8	49.5	38.2	52.6	52.6
36	31	124.00	5.6	73.5	33.0	65.0	77.5	70.0
61	32	213.00	9.7	72.0	32.0	58.2	71.6	76.0
26	32	101.50	4.6	70.5		66.0	76.0	82.5
56	33	129.50	10.0	81.5	66.0	39.2	48.8	48.8
2	33	121.75	10.0	55.5	39.3	32.6	32.8	31.7
16	34	125.25	10.0	66.5	58.2	38.8	48.2	52.6
21	35	123.00	10.0	73.0	48.3	73.8	80.0	66.0
33	37	95.00	10.0	79.0	68.0	44.2	59.0	76.5
42	40	128.00	5.8	89.0	41.6	81.0	74.1	78.2
60	41	190.25	10.0	76.0	64.5	67.0	76.5	50.2
19	42	191.25	10.0	83.0	22.5	44.5	81.4	89.0
58	42	136.25	10.0	82.5	78.0	60.2	52.0	59.0
44	45	135.75	10.0	92.0	76.0	62.5	43.0	46.5

curves only 18.6 per cent were at the lowest point at the one-half hour reading, 47.1 per cent were lowest at one hour, 21.4 per cent at two hours and 13.0 per cent at three hours. It is possible that this larger dose given subcutaneously produces a slower but more prolonged action than the intravenous dose usually described.

The average fall in the group of patients who were given 10 units of insulin was 41.8 mg per hundred cubic centimeters, while that in the 9 who were given 0.1 unit per kilogram of body weight was 41.4 mg. The drop may therefore be related more to the method of administration and the metabolism of the patient than to the size of the dose (Sevringhaus, Kirk and Heath²⁸).

Weight correlations were made because several reports have been made regarding a difference in the falls in underweight, overweight and normal subjects. The average fall was 44.5 mg per hundred cubic

centimeters for the overweight females in our group, 45 mg for the females of normal weight, 31.6 mg for the females who were underweight, 40.6 mg for the males who were overweight, 44.6 mg for the males of normal weight and 44.3 mg for the males who were underweight. This is in contrast to other figures which have shown that the sugar levels for undernourished subjects fall farther than those for normal subjects who are receiving insulin.

Fifty per cent of all the curves fell over 40 mg per hundred cubic centimeters, 41 per cent fell from 40 to 20 mg and only 9 per cent fell less than 20 mg (table 7). In distinct contrast to the results reported in the literature which lead one to expect a return to fasting or almost

TABLE 7—*Insulin Tolerance Curves, Summary*

	Drop Phase of Curve for Blood Sugar						Return Phase of Curve for Blood Sugar					
	Less Than 20 Mg		20 to 40 Mg		Over 40 Mg		Over 50%		Under 50%		No Return	
	Num	Per	Num	Per	Num	Per	Num	Per	Num	Per	Num	Per
	ber	centage	ber	centage	ber	centage	ber	centage	ber	centage	ber	centage
Males	8	7	20	49	18	44	19	46	16	39	6	15
Females	3	11	9	31	17	58	18	62	8	28	3	10
Totals	6	9	29	41	35	50	37	53	24	34	9	13

TABLE 8—*Summary of Insulin Tolerance Tests for Our Epileptic Patients*

	Number of Patients	Sugar per 100 Cc. of Blood			Standard Deviation	Coefficient of Variability
		Average Values	Median Values	Range in Values		
Fasting	71	80.5	83.2	52.6-125.0	13.0	16.2
½ hour	66	57.7	60.6	29.7-94.0	16.5	28.6
1 hour	70	52.6	48.7	22.8-93.0	16.6	31.6
2 hours	70	55.4	53.5	21.9-90.5	16.9	30.6
3 hours	70	60.3	58.6	17.0-89.0	16.7	27.8

fasting levels in ninety minutes, only 21 per cent of the 70 patients showed a 90 per cent or better return at three hours. A return of over 100 per cent was noted for 11.4 per cent, and 13 per cent did not show a return at all. Only 53 per cent returned beyond 50 per cent.

The entire picture of the insulin tolerance curve of the 70 patients is evident in an analysis of the median at each reading. From a fasting level of 83.2 mg per hundred cubic centimeters, the curve of the median drops to 60.6 mg at one-half hour and to 48.7 mg at the first hour, it returns to 53.5 mg at the second hour and to 58.6 mg at the third hour—24.6 mg below the fasting level. The last represents a 28.7 per cent failure to return (table 8).

Studies of the averages which we obtained indicate that there is a fasting level of 80.5 mg per hundred cubic centimeters, with a drop to 57.7 mg at one-half hour to 52.6 mg at one hour, to 55.4 mg at the second hour and to 60.3 mg at the third hour—a 63 per cent return

It is significant that no matter how the figures are analyzed, the greatest fall is at the first hour and the return is incomplete. When an attempt is made to correlate the low point of the curve for insulin or the return with the age, weight, state of nutrition and height or with the dextrose tolerance curve, so low a coefficient is obtained that it is evident that at least in this group no relation exists. There is no correlation between the highest sugar level after the administration of dextrose and the lowest level after the injection of insulin, or between the percentage return of the former and the percentage recovery of the latter. Nothing in the configuration of the dextrose curve is related to that of the insulin curve, e g, in patients who show a late fall in the dextrose curve below the fasting level, no rise above the fasting level occurs late in the insulin curve.

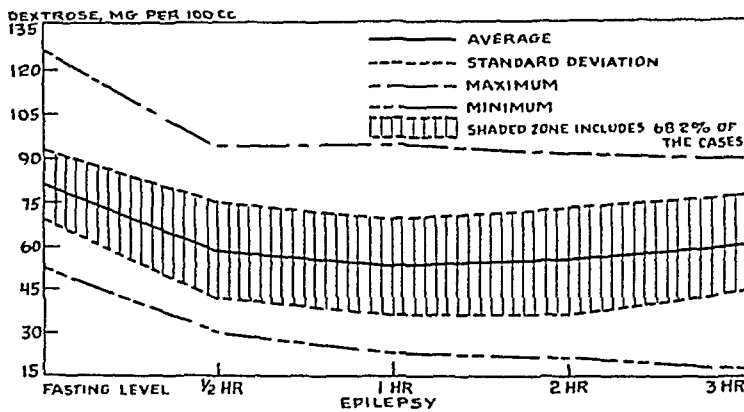


Chart 4—Insulin tolerance curves for our series of epileptic patients

The average low point for the group was 41 mg per hundred cubic centimeters, both males and females showing a similar figure. The median of the low readings for males was 40 mg and that for females was 40 mg, therefore, the same reading holds for the entire group. For the patients with organic epilepsy the figures ran somewhat lower, 37 mg being the average for the males and 33.5 mg for the females, making the average for the entire group 36.4 mg. The median was 39 mg for the males, 33.5 mg for the females and 39 mg for the entire group. The average fall for the males with organic epilepsy was 45.5 mg, for the females 49.5 mg and for the entire organic group 46.5 mg. This was higher than that for the entire group, which showed somewhat lower values—42 mg for the males, 39 mg for the females and 40.6 mg for the entire group (chart 4).

While patients who responded well to treatment showed a drop in the insulin tolerance curve to very low levels (20 mg), others showed a lack of response. There were 4 such patients. Two showed a cessation of seizures over a period of about eighteen months, while in 2 others the seizures occurred as before. All other attempts to utilize

the insulin tolerance curve or any part of it as a clue to whether or not a patient would do well met with failure. Nothing in the insulin tolerance curve, as in the case of the dextrose tolerance curve, could be used as a prognostic index.

HYPOGLYCEMIA AND THE CONVULSION IN EPILEPSY

The observation of convulsions resulting from a decrease in the sugar content of the blood after an injection of insulin and the discovery of cases of hyperinsulinism with convulsions, due to tumors in the pancreas, led to the assumption that the hypoglycemic state can precipitate convulsions in epilepsy. Harris³⁶ has stated that in more and more cases convulsive disorders will be found to be manifestations of hypoglycemia. Griffith³⁷ found low values for blood sugar for patients with convulsions and drew a similar inference.

As stated previously, Baudouin and Azerad, despite the marked hypoglycemia produced in some cases, said they were unable to produce either convulsions or attacks of petit mal by the injection of insulin in epileptic patients.

One must keep in mind that the lower the dextrose reading is below about 60 mg per hundred cubic centimeters, the greater the error in the measurement. The blue color becomes so faint that it is hard to match it even with comparable known standards. Yet when readings are down in this questionable zone, they emphasize the fact that these patients are in a hypoglycemic state.

Fifty-five of our 70 patients showed levels below 50 mg of sugar. One value was so low as to be unreadable, 1 stood at 17 mg, 3 between 20 and 25 mg and 28 between 30 and 39 mg. Yet none of the patients showed signs of seizure when the values were at these levels. The quantitative readings of the bromide content of the blood were sufficiently low to enable one to say that convulsions were not prevented as the result of medication. Many of the patients were not receiving any medication. In 7 instances attacks appeared from two to twelve hours after the hypoglycemic state developed. All these patients had been having attacks independent of the injections of insulin.

It appears, therefore, that acutely induced hypoglycemic states do not precipitate epileptic seizures.

Harris, extending his idea that hyperinsulinism is the cause of some cases of epilepsy, suggested that bromides inhibit the secretion of insulin. We have therefore correlated the amount of bromide in the blood of our patients with the amount of sugar in the blood during fasting and the character of the dextrose tolerance curve.

³⁶ Harris, Seale. Epilepsy and Narcolepsy Associated with Hyperinsulinism, *J A M A* **100** 321 (Feb 4) 1933.

³⁷ Griffith, J P C. Hypoglycemia and the Convulsions of Early Life, *J A M A* **93** 1526 (Nov 16) 1929.

In 28 cases a determination of the bromide content of the blood was made at the same time as the sugar study. Despite the fact that many of the patients showed a high level of bromide in the blood (up to 300 mg per hundred cubic centimeters), the fasting level for sugar for the group or for an individual patient showed no departure from that of the rest of the patients.

CONCLUSIONS

The fasting levels for dextrose of a series of 90 patients suffering from epilepsy were within normal limits. There was no relation between this level and the age, weight or sex.

There was no relation between the fasting levels for sugar and the precedence of succession of attacks, nor could the levels be correlated with the type of epilepsy, organic or idiopathic.

Oral dextrose tolerance tests were performed with blood from the finger for 90 of these patients. The readings fell essentially in the normal zone. Twenty-six per cent were high, 21 per cent low and 53 per cent normal. The same lack of correlation noted in the sugar studies during fasting was observed here. There was no evidence of an increased or decreased tolerance.

Further work on large groups of normal subjects is indicated to determine the significance of the various curves obtained in the dextrose tolerance tests. It is possible that when such studies are made, the variability of our curves may assume some importance in relation to a possible defective homeostasis of the body to dextrose stimulation.

Glycosuria occurred during the dextrose tolerance test in 20 per cent of the cases. There was none at fasting levels. The renal threshold for our patients averaged 188 mg of blood sugar. This is slightly above that given for normal subjects. There was no evidence of a decreased tolerance.

Insulin tolerance tests performed by the subcutaneous method on 70 patients revealed a tendency for the lowest level to be attained at the end of the first hour and a distinct failure for the curve to return at the end of the third hour. No correlations with the age, weight, type of epilepsy, etc., could be found in the response of the patients to insulin.

The insulin tolerance test seems to indicate a failure of homeostasis because of the relatively many instances in which there was a failure to return at all after three hours. These curves should be compared with others subsequently obtained in large series of normal subjects.

A hypoglycemic state produced in 70 patients failed to precipitate an epileptic seizure.

Concentration of bromide in the blood at high or low levels failed to produce any alteration in the level of the blood sugar.

RETENTION AND UTILIZATION OF SMALL AMOUNTS OF ORALLY ADMINISTERED IRON

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It has been demonstrated repeatedly that a satisfactory hemoglobin response in cases of hypochromic anemia ensues with the administration of large amounts of iron,¹ but it is recognized that the amount of iron so administered is greatly in excess of that utilized in hemoglobin regeneration. We² have shown that from 14 to 71 per cent of the administered iron is retained by the body when 3 Gm of iron and ammonium citrates (yielding approximately 500 mg of metallic iron) is given daily by mouth. Only a small portion of this (12 to 34 per cent) is utilized in the building of hemoglobin.

The hemoglobin response to small amounts of iron has been found to be less satisfactory, although the amount of iron would seem to be adequate for hemoglobin regeneration if it were properly absorbed from the gastro-intestinal tract. The present study was undertaken to determine the amount of iron retained when these more moderate doses of iron and ammonium citrates were administered. Balance studies were conducted, as described in a previous communication.² For a three day period of adjustment before observations were begun, the patients were given the diet which they were to receive throughout the period of study. This was followed by a control period, during which no medicinal iron was administered and the intake of iron was obtained from the food alone. This period and all subsequent ones were of six days' duration.

Supported in part by a grant from Eli Lilly & Co.

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This work was begun in association with Dr C W Baldridge, who died on Nov. 22, 1934.

1 Bethell, F H, Goldhamer, S M, Isaacs, R, and Sturgis, C C. The Diagnosis and Treatment of the Iron-Deficiency Anemias, *J A M A* **103** 797 (Sept 15) 1934. Meulengracht, E. Large Doses of Iron in the Different Kinds of Anemia in a Medical Department, *Acta med Scandinav* **58** 594, 1923. Goodall, A. Treatment of Anemia Chlorosis and Secondary Anemia, *Lancet* **1** 1216, 1926.

2 Fowler W M, and Barer, A P. Retention and Utilization of Orally Administered Iron, *Arch Int Med* **59** 561 (April) 1937.

The essential clinical features and the hematologic data for each patient are given in tables 1 and 2. A minimal tuberculous lesion was found in the apex of the left lung of patient 1 on roentgenologic examination, but it seemed unlikely that anemia of this degree would be produced by otherwise asymptomatic tuberculosis. No history of excessive loss of blood was obtained. In patient 6 the anemia was apparently idiopathic in origin, while in the other four patients it was undoubtedly due to a chronic loss of blood.

TABLE 1—*Clinical Features*

Patient	Age	Sex	Diagnosis	Clinical Features
1	40	F	Hypochromic anemia	Minimal pulmonary tuberculosis in apex of left lung
2	23	F	Hypochromic anemia, hemorrhage	Profuse menstrual bleeding for several years, submucous fibroid tumor removed
3	33	F	Hypochromic anemia, hemorrhage	Gross hematuria with "fish worm" clots for two years after blow on abdomen, no history of other loss of blood, pyelograms revealed crossed ectopic fused kidney, no other cause for anemia found, hematuria ceased spontaneously
4	21	F	Hypochromic anemia, hemorrhage	Profuse uterine bleeding, cervical polyp removed, hyperplastic endometritis
5	44	F	Hypochromic anemia, hemorrhage	Profuse menstrual bleeding, hysterectomy performed for fibromyoma
6	46	F	Hypochromic anemia, idiopathic	Migraine, splenomegaly, visceroptosis, normal renal function, normal basal metabolic rate, achlorhydria

TABLE 2—*Hematologic Data*

Patient	Hemo- globin, Percentage	Hematocrit Reading, Percentage	Erythro- cytes, Percentage	Color Index	Volume Index	Satura- tion Index	Gastric Acidity	Basal Metabolic Rate
1	50	77	83	0.60	0.92	0.64	0	-16
2	46	73	68	0.67	1.07	0.63	Normal	-9
3	25	40	56	0.44	0.71	0.62	Normal	+5
4	55	70	62	0.88	1.12	0.78	Normal	+1
5	52	61	82	0.63	0.74	0.85	0	-18
6	54	63	87	0.62	0.72	0.85	0	-2

The results of the iron balance studies, together with the nitrogen and phosphorus balances, are given in table 3, and a summary of the iron studies is given in table 4. The first five patients received from 170 to 180 mg of iron per day, which represented the administration of approximately 5 grains (0.3 Gm) of iron and ammonium citrates three times daily, given as an aqueous solution of the brown scales. Patient 6 received 7½ grains (0.48 Gm) of the drug three times daily, with an average daily intake of iron of 243.5 mg.

All the patients were in negative iron balance during the control period, but with the administration of iron and ammonium citrates iron was retained in every instance. The amount retained, as might be expected, was much less than that retained by those patients previously

reported on ² who had received larger amounts of the drug. The daily retention of iron varied from 26.2 to 114.4 mg. All the patients were in positive iron balance continuously, but the retention in the first period was somewhat greater than during the second six-day period. Patient 4 retained 1,479.9 mg of iron in eighteen days, and patient 5 retained 1,074.6 mg in twenty-four days. The percentage of the administered iron which was retained by the body varied from 10.3 to 45.1, with

TABLE 3—*Nitrogen, Phosphorus and Iron Balances*

Patient	Period	Nitrogen, Mg			Phosphorus, Mg			Iron, Mg			Red Blood Cells, Mil lions	Hemo globin, Gm per 100 Cc
		In take	Excre- tion	Bal- ance	In take	Excre- tion	Bal- ance	In take	Excre- tion	Bal- ance		
1	1	9.78	11.12	-1.34	1.44	1.18	+0.26	11.9	18.5	-6.6	4.12	7.188
	2	9.85	10.72	-0.87	1.43	1.16	+0.27	180.5	125.3	+55.2	4.13	7.393
2	1	10.77	10.82	-0.05	1.53	1.23	+0.25	13.0	25.7	-12.7	3.50	6.273
	2	11.65	9.81	+2.04	1.62	1.37	+0.25	182.7	139.5	+43.2	3.77	6.345
3	1	10.73	11.54	-0.81	1.55	1.32	+0.23	13.0	25.9	-12.9	2.73	4.150
	2	11.64	7.00	+4.64	1.60	1.76	+0.16	182.6	139.4	+43.2	3.03	4.680
4	3	13.34	7.01	+6.33	1.85	2.01	-0.16	183.9	141.8	+42.1	3.58	5.355
	1	10.37	5.60	+4.77	1.50	1.33	+0.17	12.7	22.2	-9.5	3.19	7.800
5	2	11.04	5.26	+5.78	1.55	1.59	-0.04	182.0	111.0	+71.0	3.56	7.800
	3	11.04	5.86	+5.18	1.55	1.37	+0.18	182.0	120.8	+61.2	3.99	9.020
6	1	11.04	6.07	+4.97	1.55	1.45	+0.10	182.0	67.6	+114.4	4.08	10.520
	2	9.96	10.20	-0.24	1.42	1.38	+0.04	10.2	14.5	-4.3	4.22	7.365
7	3	9.97	9.55	+0.42	1.42	1.13	+0.29	170.6	117.3	+53.3	4.40	8.005
	5*	9.95	10.11	-0.16	1.43	1.57	-0.14	170.7	156.4	+14.3	4.25	8.340
8	1†	9.97	11.76	-1.79	1.42	1.43	-0.01	170.6	105.2	+65.4	4.68	10.370
	5	9.97	11.72	-1.75	1.42	1.19	+0.23	170.6	122.0	+48.6	4.93	11.360
9	1	9.94	0.48	+9.46	1.18	0.92	+0.26	10.0	10.7	-0.7	5.02	7.710
	2	10.08	9.43	+0.65	1.18	0.86	+0.32	253.5	227.3	+26.2	4.71	7.440

* Five-day period.

† Thirty-six days between periods 3 and 4. Medication was continued.

TABLE 4—*Average Daily Iron Balances by Periods*

Patient	Iron Balance, Mg					Total Iron Retained, Mg	Average Daily Retention of Iron, Mg
	Control Period	Period 1	Period 2	Period 3	Period 4		
1	-6.6	+55.2				330.7	55.2
2	-12.7	+43.2				259.3	43.2
	-12.9	+43.2	+42.1			511.8	42.6
4	-9.5	+71.0	+61.2	+114.4		1,479.9	82.8
5	-4.3	+53.3	+14.3	+65.4	+48.6	1,074.6	44.7
6	-0.7	+26.2				156.8	26.2

an average retention for the six patients of 26.6 per cent. This is slightly lower than the average of 32.6 per cent reported for the group of patients receiving 500 mg of iron per day,² but the difference is not great enough to be of significance.

The severity of the anemia did not play a part in determining the amount of iron retained. The two patients showing the highest and the lowest percentage of retained iron had almost identical readings for hemoglobin, and the patient with the lowest value for hemoglobin retained slightly less iron than the average for the entire group.

It is recognized that adequate control periods and absence of recent loss of blood are necessary in attempting to evaluate the effectiveness of iron in hemoglobin regeneration, and these factors were given due attention in selecting the patients for this study. The usual reticulocyte response was obtained after the administration of iron, and the rate of hemoglobin regeneration was satisfactory. Patients 1, 2 and 6 are not considered in this connection, since they received iron for only one six day period, a period too short to be of significance in considering hemoglobin regeneration with orally administered iron. For the remaining three patients the daily increase in hemoglobin was 0.1, 0.151 and 0.082 Gm per hundred cubic centimeters of blood, respectively. This falls short of the optimum hemoglobin response given by Heath³ but nevertheless is satisfactory in view of the small amount of iron administered to these patients.

TABLE 5—Retention and Utilization of Iron

Patient	Total Intake of Iron, Gm	Total Iron Retained, Gm	Original Hemoglobin Content, Gm per 100 Cc	Total Increase in Hemoglobin, Gm	Average Daily Gain in Hemoglobin, Gm per 100 Cc	Iron, Percentage Retained	Iron, Percentage Used as Hemoglobin	Retained Iron Percentage Used as Hemoglobin
1	1.082	0.330	7.18			70.5		
2	1.096	0.259	6.27			23.6		
3	2.193	0.511	4.15	60.25	0.100	23.2	8.2	35.3
4	3.276	1.479	7.80	136.00	0.151	15.1	12.4	27.5
5	3.923	1.074	7.36	98.25	0.082	27.1	7.5	27.1
6	1.520	0.156	7.71			10.3		

If it is assumed, as it was by Heath,³ that the volume of blood in each case was 5 liters and if the approximate total gain in hemoglobin is calculated for each, it is found that from 7.5 to 12.4 per cent of the orally administered iron was used in the formation of hemoglobin (table 5). The average for the three patients was 9.3 per cent which is considerably larger than the 1.9 per cent utilized when large amounts of iron were administered² and is greater also than the 3.4 per cent reported by Heath. Of the iron which was retained by the body, it was found that 30 per cent was used in the formation of hemoglobin. The remaining 70 per cent was presumably stored in the spleen, liver and other parts of the reticulo-endothelial system.

COMMENT

One is not justified in assuming, on the basis of the three patients studied in respect to hemoglobin regeneration, that these small amounts of iron are sufficient to produce a satisfactory hemoglobin response in

³ Heath, C. W. Oral Administration of Iron in Hypochromic Anemia, Arch. Int. Med. 51:459 (March) 1933.

all patients. It does show, however, that in certain uncomplicated cases this amount of iron will suffice both for a satisfactory increase in hemoglobin content and for a replenishment of the depleted stores of iron. In all the cases a sufficient amount of iron was retained to supply the needs of the body in this respect. The amount of iron retained was much less than that with the administration of 3 Gm of iron and ammonium citrates per day, but the average daily positive balance of from 143 to 1144 mg was sufficient for the body requirements, even with the abnormal demands resulting from prolonged anemia. The percentage of the iron utilized in the formation of hemoglobin was somewhat greater than with the larger intake of iron, although such comparisons may be misleading, since many factors other than the retention of iron may influence hemoglobin regeneration. The percentage of the retained iron which was utilized in the formation of hemoglobin is interesting, as it shows that a large part of the iron is deposited in the body in some form other than hemoglobin. A considerable portion is presumably used to replenish the depleted stores of iron, since animal experimentation has shown that the iron content of the reticulo-endothelial system is increased after the administration of iron.⁴ Although abundant iron is available for its formation, hemoglobin regenerates more slowly than with the administration of larger amounts of iron. The reason for this is not apparent. Whipple⁵ has asserted that the excess iron from larger doses exerts a "salt effect." It has been assumed also that iron may act as a direct stimulant of bone marrow, although definite proof of this is lacking.

If the administration of large amounts of iron over a long period has caused some concern as to its possible deleterious effect on the body, it is of interest to note that an adequate amount can be retained from smaller doses. Massive doses seem to be advisable early in the course of therapy, because of the more rapid hemoglobin response, but for a maintenance dose smaller amounts suffice, and they lessen the potential danger from prolonged massive doses.

SUMMARY

The administration by mouth of iron and ammonium citrates in doses of 1 and 1.5 Gm daily leads to the retention of iron in such amounts as will replenish the depleted stores of iron and produce a fairly rapid increase in the hemoglobin content.

4 Polson, C. J. The Storage of Iron Following Its Oral and Subcutaneous Administration, *Quart J Med* **23** 77, 1929. Robscheit-Robbins, F. S. The Regeneration of Hemoglobin and Erythrocytes, *Physiol Rev* **9** 666, 1929.

5 Whipple, G. H., and Robscheit-Robbins, F. S. Blood Regeneration in Severe Anemia. Optimum Iron Therapy and Salt Effect, *Am J Physiol* **92** 362, 1930.

COCCIDIOIDES INFECTION

PART I

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Because the first known case in North America of what is now called coccidioidal granuloma was reported from Cooper Medical College, in San Francisco, by Rixford and because the disease was proved by Ophuls, also of Cooper Medical College, to be caused by infection with a pathogenic fungus and not with a protozoan organism, coccidioidal granuloma has always aroused much interest in that school, which later became the Stanford University School of Medicine. Many patients with coccidioidal granuloma, representing practically all the known clinical types of the disease, have been studied and treated in the hospitals of this institution. For many years there has been more or less intensive study of the fungus in the laboratories of the medical school.

The generally accepted conceptions of the disease have gradually changed during the past thirty years, from the time when the disease was believed to be very rare and almost always fatal until the present, when about thirty new cases are reported to the State Department of Health in California each year, with a reported mortality rate during the past eight years of only 49.7 per cent. In all, four hundred and fifty cases have been reported in California.

The reports that will follow are based on a study of infection with *Coccidioides* in human beings and domestic animals in California, supplemented by intensive experimental work which has been conducted during the past few years.

The number of articles on coccidioidal granuloma published in the medical literature of the United States is relatively great in proportion to the number of known cases in this country. The first case reported was from Buenos Aires in 1892.¹ The first report of a case in North America (California) was made in 1894.² A number of cases

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1 Wernicke, R. Ueber einen Protozoenbefund bei Mycosis fungoides (?), *Centralbl f Bakt* 12 859, 1892.

2 (a) Rixford, Emmet. A Case of Protozoic Dermatitis, *Occident M Times* 8 704, 1894. (b) Rixford, Emmet, and Gilchrist, T. C. Two Cases of Protozoan (Coccidioidal) Infection of the Skin and Other Organs, *Johns Hopkins Hosp Rep* 1 209, 1896.

have been reported from Colombia and Brazil of a similar infection with fungus which has been described as *Paracoccidioides* by de Almeida,³ who named the organism *Coccidioides brasiliensis*. Several reports have appeared in the British and European medical literature, but they have dealt almost exclusively with cases which had occurred in North or South America.

The great majority of the articles published in this country have been case reports and have suggested methods of therapy, usually unsuccessful. A few authors in the United States, notably Ophuls,⁴ Ricketts,⁵ Wohlbach,⁶ MacNeal and Taylor⁷ and Ahlfeldt,⁸ have made careful studies of the fungus *Coccidioides* and have attempted to correlate the peculiar endosporulating spherules which are found within the tissues with the fine septate mycelial growth which develops on the culture medium.

The mortality rate in cases reported in the United States has been high, but this has undoubtedly been due to the fact that, for the most part, only cases of advanced stages of the disease have been recognized, and until recently only the cases of severe and fatal involvement have been described in the literature. It is a fact that when the infecting agent has become disseminated in the body, a severe generalized infection, with multiple lesions in various parts of the body, develops and usually progresses rapidly until the death of the patient. In 1905 Ophuls⁹ reported on twelve patients, of whom ten were dead and one had been lost sight of at the time of the report. When I¹⁰ reported on a col-

3 de Almeida, F. P. Estudos comparativos do granuloma coccidioidica nos Unidos e Brasil. Novo genero para o parasito brasileiro, Ann Fac de med de São Paulo **5** 125, 1930, abstr, Compt rend Soc de biol **105** 315, 1930.

4 (a) Ophuls, William, and Moffitt, H. C. A New Pathogenic Mould (Formerly Described as a Protozian, *Coccidioides Immitis*, *Pyogenes*), Philadelphia M. J. **5** 1471, 1900. (b) Ophuls, William. Further Observations on a Pathogenic Mould Formerly Described as a Protozoan (*Coccidioides Immitis*, *Coccidioides Pyogenes*), J. Exper. Med. **6** 443, 1905.

5 Ricketts, H. T. Oidiomycosis (Blastomycosis) of the Skin and Its Fungi, J. M. Research **1** 373, 1901.

6 Wohlbach, S. B. The Life Cycle of the Organism of "Dermatitis *Coccidioides*," J. M. Research **13** 53, 1904.

7 MacNeal, W. J., and Taylor, R. M. *Coccidioides Immitis* and Coccidioidal Granuloma, J. M. Research **30** 261, 1914.

8 Ahlfeldt, Florence E. (a) Studies in Coccidioidal Granuloma, Arch. Path. **2** 206 (Aug.) 1926, (b) Special Observations on the Morphology of *Coccidioides Immitis*, J. Infect. Dis. **44** 277, 1929.

9 Ophuls, William. Coccidioidal Granuloma, J. A. M. A. **45** 1291 (Oct. 28) 1905.

10 Dickson, E. C. Oidiomycosis in California, with Especial Reference to Coccidioidal Granuloma. Arch. Int. Med. **16** 1028 (Dec.) 1915.

lection of forty cases in 1915, I made the statement that "the prognosis is extremely grave. The outcome of the disease is almost always fatal." The same opinion has been expressed by many authors. In my report in 1915, however, were recorded two cases in which early amputation or resection of local lesions in the extremities was followed by clinical recovery and one case in which a healed or arrested lesion was discovered at autopsy in the lung of a man who had died of carcinoma of the stomach. Similar healed or arrested lesions in the lungs have since been observed at autopsy in a number of patients in Stanford University and other hospitals, so that there can be no doubt that the lesions of coccidioidal granuloma have a tendency to heal. Moreover, one occasionally encounters patients with more or less localized lesions, more often in the skin, in whom the course of the disease is stationary, sometimes for years, although such lesions rarely heal spontaneously.

More recently, observations have been made which indicate that there is much to learn about the initial manifestations of infection with *Coccidioides*. In 1929 I was afforded an excellent opportunity of studying, with Dr. P. H. Pierson, of the Stanford University Hospital, two patients with primary pulmonary infection. One of the patients had acquired the infection in our laboratory, and the other, an engineer, had acquired it in the oil fields of the San Joaquin Valley, where he had been exposed to a great deal of dust when engaged in construction work. Both patients had bronchopneumonia of moderate severity, and roentgenographic examination showed that the involvement was more intense in the bases of the lungs (fig. 1). In one instance the first diagnosis made by the roentgenologist was tuberculosis. The diagnosis of infection with *Coccidioides* was established in both cases by demonstration of the typical spherules of *Coccidioides* in the sputum, confirmed by culture and guinea-pig inoculation. After severe illness and protracted convalescence, both patients recovered, apparently completely, and have shown no subsequent indication of the infection. We have knowledge of two other patients who had a similar history, one of whom, described by Boyers,¹¹ has remained well for at least fifteen years. The later history of the other patient is unknown to us.

Another fact that has become evident is that in a number of instances in which the first manifestation of illness has been an acute "cold" or bronchopneumonia, this has been followed shortly by an outbreak of erythema nodosum, usually on the shins. I recently saw three patients with such acute involvement: the young man who acquired the infection in our laboratory, a student who spent his vacation working in an area where the disease is endemic and a woman who was

11 Boyers, L. M. Therapy in Two Cases of Infection with *Coccidioides*. *Fungus*, M. Herald **52** 61, 1933.

visiting in an area where the disease is endemic. The diagnosis was made in the first case as previously described, in the second by microscopic examination of biopsy tissue from a lesion on the neck and in the third by means of a cutaneous test with coccidioidin about two months after subsidence of the acute illness. The roentgenograms in the third case, like those in the case of laboratory infection previously mentioned, showed pulmonary involvement which at first was believed to be tuberculous, but after later examinations the roentgenologist concluded that the involvement could not be tuberculous because the lesions were clearing rapidly.

Dr Merrie Gifford, of Bakersfield, Calif., has shown me records of three of fifteen patients with coccidioidal granuloma, admitted consecutively to the Kern County Hospital, in whom the first sign of illness was a "bad cold" with a cough or bronchopneumonia, associated with erythema nodosum. In all these patients there had been progression

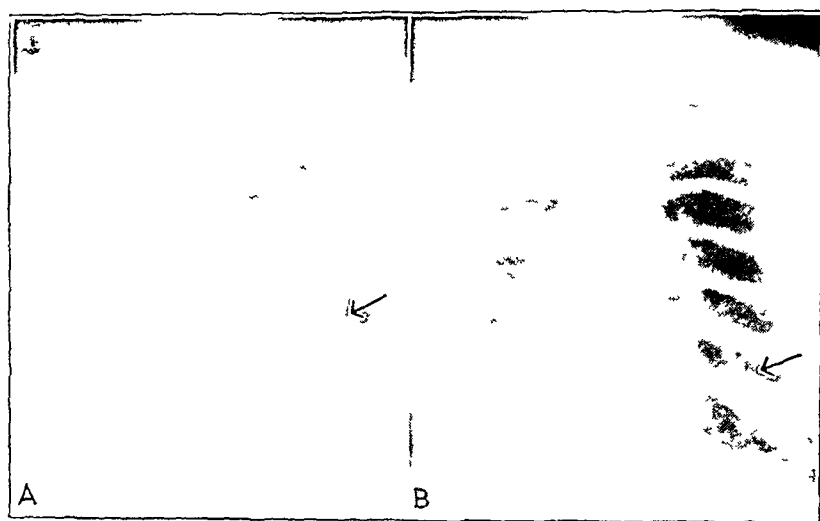


Fig 1—Roentgenograms of the chest in case 1. *A*, at the onset of illness on Sept 18, 1929. Note the increased density toward the base of the left lung. *B*, one month later. Note that the basal infiltration is much less dense.

to the later stages of coccidioidal granuloma with disseminated lesions, but, according to Dr Joe Smith, Health Officer of Kern County, erythema nodosum, often accompanied with a severe cold, is unusually common in San Joaquin Valley, there is a characteristic seasonal incidence and many of the patients recover promptly. The first of our patients with erythema nodosum is well after more than six years, one of the two patients recently seen shows no signs of the acute illness other than the clearing lesions in the lungs, but the third still shows involvement of the cervical lymph nodes.

It is obvious, therefore, that more information concerning the earliest manifestations of coccidioidal granuloma in human beings and

of the method of spread of the fungus in the tissues is urgently needed. Evidence is accumulating that death from coccidioidal granuloma occurs only when there is the extensive involvement of the tissues which follows dissemination of the organism in the blood stream and that heretofore only this late disseminated type has been generally recognized. In my opinion, one would be equally justified in drawing all conclusions of tuberculosis from a study of cases of acute military involvement in which the tubercle bacilli have been widely disseminated by the blood stream as in basing all knowledge of coccidioidal granuloma on terminal stages in which the organisms have become widely disseminated. Since it is known that lesions of coccidioidal granuloma may be very sluggish, that there is a definite tendency for the lesions to heal and that at least some of the victims of the infection recover or at least remain free from symptoms for several years, it is essential that attempts be made to learn more of the initial manifestations of infection with this organism and that judgment be reserved as to the true incidence of the disease until more information along these lines is at hand.

The fact that almost all the patients in whom early infection with *Coccidioides* has been recognized had initial "colds" or bronchopneumonia tends to substantiate the stated belief of Ophuls and others that the disease is usually acquired by inhaling the spores of the fungus. That inhalation of the spores may cause the onset of acute infection was shown, almost with experimental precision, in the case of the young man who acquired the disease in our laboratory. The exact time of the exposure was known, it occurred on the first day he was permitted to work with the fungus. By an unfortunate mistake he removed the cover from a Petri dish containing an old, partially dried culture of *Coccidioides* and observed a fine brownish cloud rise from the culture. Ten days later he had a "cold" which progressed to bronchopneumonia. This hypothesis has been supported by the fact that Beck, Traum and Harrington¹² found that in infected cattle the bronchial and mediastinal glands, and usually only these, are involved. Moreover, necropsy in human beings often shows that the peribronchial lymph glands reveal an old chronic type of lesion which contrasts sharply with the more recent types of lesions observed elsewhere. These older lesions obviously antedate the more recent lesions which are distributed generally throughout the body. It is not difficult to believe that they are produced by lymph draining from acutely infected lungs in which the lesions subsequently clear and that they constitute the foci in which the infective agent persists in the body and is eventually disseminated by involvement of a blood vessel.

¹² Beck, D., Traum, J., and Harrington, E. S. Coccidioidal Granuloma Occurrence in Animals, *J. Am. Vet. M. A.* **78**: 490, 1931.

Of course cases have been reported in which it seemed certain that cutaneous lesions were primary, owing to local inoculation with the spores of the fungus. The first case described by Rixford²¹ was that of a laborer who had a verrucous lesion on the back of the neck, where his collar band rubbed, that persisted for eight years before it began to spread to any great degree. In case 33 which I described in 1915,¹⁰ the first lesion was at the site of an abrasion on the hand which was caused by picking walnuts. Seilin¹³ reported the case of a cigar maker who had a lesion on the hand and who apparently showed no signs of systemic involvement. Guy and Jacob¹⁴ described a case in which, after a prick on the thumb with a cactus spine, the first small abscess developed at the site of the puncture and was followed by a number of similar lesions along the track of the lymphatics until the axilla was reached. It was only later that the patient presented evidence of general dissemination of the parasite. However, the appearance of the first visible lesion on the skin does not necessarily mean primary involvement of the skin. In the case of the student in our series of patients showing acute involvement, the first demonstrable lesion after the acute onset was a small "pimple-like" pustule in the skin of the neck from which spherules of *Coccidioides* were isolated.

In commencing our study of the manner of spread in infection with *Coccidioides* it seemed desirable to review the reported observations on the characteristics of the fungus on culture medium and in infected subjects. This part of the work was carried through by Dr. H. D. Chope, of Newton, Mass., when he was a member of this department. His method of procedure differed from the methods that had previously been reported in that he made a more detailed study of individual spherules which were isolated from pus and injected the fungus into the testicles of guinea-pigs in order to observe the various changes which occur in animal tissues.

When Posadas discussed Weirnicke's case¹⁵ and Rixford and Gilchrist² reported their cases, they described carefully the peculiar spherules and method of endosporulation. They stated the opinion that they were dealing with a protozoon of the *Coccidia* type, hence the name *Coccidioides*. Ophuls and Moffitt^{4a} discovered that the infecting organism is not of the animal kingdom but a fungus with a characteristic production of endosporulating spherules within the tissues, although it grows on culture medium as a mass of fine septate mycelium.

13 Seilin, J. Report of a Case of Dermatitis Coccidiosa, *M. Rec.* **95** 360, 1919.

14 Guy, W. H., and Jacob, F. M. Granuloma *Coccidioides*, *Arch. Dermat. & Syph.* **16** 308 (Sept.) 1927.

15 Posadas, Alexandre. Psorospermiose infectante generalisee, *Rev. de chir.* **21** 277, 1900.

The mature spherules in the tissues average about 30 microns in diameter, although young forms may be much smaller and some endosporulating forms may be considerably larger. The outer wall is a thick, hyaline, double-contoured capsule which in some instances may be covered with spines or, better, prickles. Reproduction within the tissues is always by endosporulation, never by budding, the endospores being liberated by rupture of the capsule, which remains as an empty "envelop." When pus is evacuated and planted on culture medium or when the pus is allowed to stand in a container, mycelia develop from the spherules and form the mold growth previously mentioned. However, development of hyphae never takes place within living animal tissue, and maturation of the spherule with endospores has never been observed except in living animals.

If one begins with the spherule which occurs in pus, what one may describe as the first, or vegetative, phase in the various stages of development is the development of hyphae to form the mold growth. Ophuls^{4b} reported this in detail in 1905. He studied the development of individual spherules suspended in broth in hanging drop preparations. His description was as follows:

The thick membrane which surrounds the latter [spherule] becomes very thin in one place and begins to evaginate over the bud from the enclosed protoplasm. These buds soon assume the form of coarse, more or less cylindrical threads which are either straight or somewhat wavy. At first the protoplasm forms one continuous mass in the main body [of the spherule] and buds, but after a while septa appear at various places in the buds, and sometimes partitions also form between the bud and the main body.

Wohlbach⁶ stated that the mycelia sprout from the capsule, but MacNeal and Taylor⁷ and Chope said they agreed with Ophuls that they begin as evaginations of the protoplasm through the capsule. Chope also observed instances in which the sprouting filaments could be seen originating from the endospores in pus before they had been released from the mother spherule (fig 2*d*), but of course the pus had been evacuated, as no indication of hypha formation has ever been observed until after the spherules have been removed from the animal body. The formation of hyphae is as specifically limited to the growth of the organism on medium outside the body as reproduction by endosporulation is restricted to development within the tissues.

As was pointed out by Ophuls,⁹ all spherules do not sprout hyphae, but there is nothing definite by which a spherule that will form hyphae can be distinguished from one that will not. Ophuls stated the belief that they must be mature. Ahlfeldt^{8b} described minute bodies in the compartments of mycelium from which the spherules are formed, which suggested sexual elements and the possibility of a bisexual life, but she

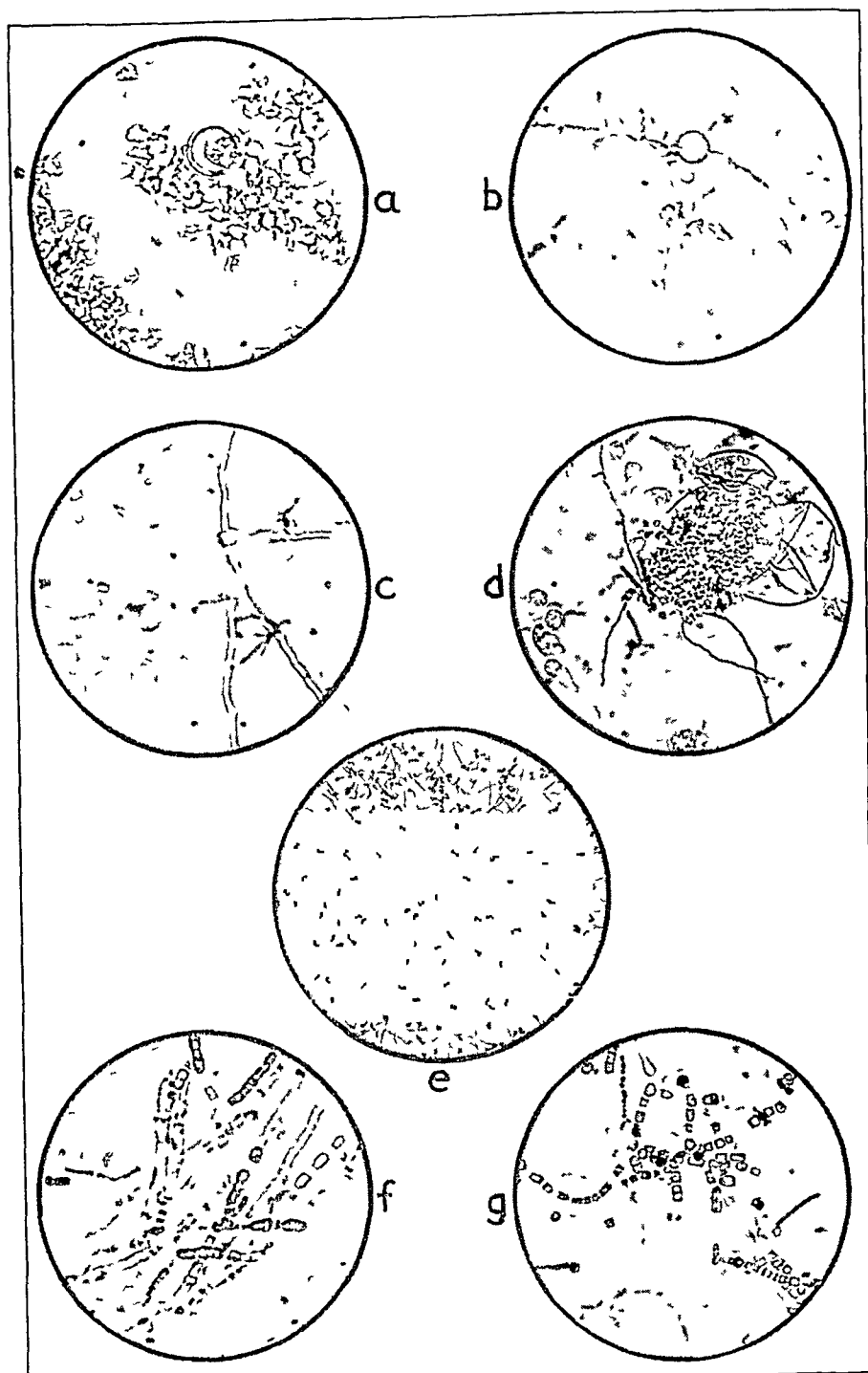


Fig 2—Section *a* shows a spherule of *Coccidioides* in pus, *b*, mycelia growing from the spherule, *c*, mycelia growing from a free endospore, *d*, mycelia growing from endospores which have recently burst the capsule but have not been dispersed, *e*, a portion of the growth, *f*, mycelia, with the formation of septums and the beginning of chlamydospore formation, and *g*, well formed chlamydospores some of them broken free from the mycelium

did not observe conjugation. I have not seen anything that would support such a theory either in mycelial segments or in the spherules.

When the spherule has sprouted and produced branching mycelia, growth occurs on culture medium as a mold, presumably identically as it develops in nature. The organism will maintain its type and virulence for years when transplanted to new medium from time to time. Passage through an animal with a cycle of spherule formation does not appear to be necessary for the survival of the organism. Certain cultures have been maintained in our laboratory for at least ten years by simply transferring the organisms to new medium from time to time, and they do not seem to have lost any of their infectivity or virulence for laboratory animals in that time.

In both the fungus grows near the bottom of the test tube as white fluffy balls consisting of an intricate meshwork of fine branching mycelium. On an agar plate it may develop into a discrete round fluffy colony, 2 inches (6 cm) or more in diameter. On agar slants it occurs first as small white nodules made up of branching hyphae which soon coalesce until the whole surface of the medium is covered with the fluffy white growth, which has numerous fine mycelia penetrating the medium and firmly anchoring it. As the culture ages the growth becomes more brownish, gradually the fluffy appearance is lost and the culture appears as a somewhat membranous cover over the medium, which is finely granular—as if dusted with fine flour. These old cultures are particularly dangerous to handle, as the fine deposit consists of light chlamydospores that are readily disseminated through the air. It was such a dissemination which was observed when the cover was removed from a Petri dish culture by the young man who became infected in our laboratory.

The optimum temperature for the sprouting of the spherules appears to be about 30 C, but thereafter the growth of the fungus appears to be somewhat more luxuriant at 37 C. No sprouting or growth was observed at 42.5 C. Pus which contains spherules may be left in the icebox for two months without any sprouting of the spherules, but if the spherules are then placed at 30 or 37.5 C they sprout promptly and there does not seem to be anything remarkable about the growth which results.

The fungus grows readily on practically all the ordinary culture mediums and usually is not overgrown by bacteria, although the bacterial growth may be active for almost two days before the colonies of fungus appear. Growth occurs also, although less actively, on synthetic inorganic mediums.

Coccidioides has never been observed in nature. On one occasion Stewart and Meyer¹⁶ succeeded in isolating it from soil secured in an

16 Stewart, R. A., and Meyer, K. F. Isolation of *Coccidioides Immitis* (Stiles) from the Soil, *Proc. Soc. Exper. Biol. & Med.* **29** 937, 1932.

area where the disease is endemic, but its habitat in nature is unknown. It is suspected that the infectivity for human beings and animals depends on its growth in regions where in winter there is rain, with relatively little cold, and where the summers are dry, permitting the distribution of chlamydospores with dry soil which is stirred up as dust.

The formation of chlamydospores is as follows, as described by Ophuls^{1b}: first the division of the aerial hyphae into segments by firm partitions, then the development of thickened capsules and finally the separation by fragmentation of the now brittle hyphae. When the chlamydospores are liberated, they occur singly or in groups which may remain attached to each other by the persisting portions of the hyphae which connect them. If these chlamydospores are transferred to fresh medium, mycelia promptly sprout, and new colonies are formed. The first phase of the development is shown in figure 2.

The second, or parasitic, phase of development, that of the formation of spherules in the tissues, has been described by Ophuls,^{1b} Wohlbach⁶

*Results of Inoculations with Different Cultures **

Day After Inoculation on Which Animal Was Killed	Age of Culture					
	2 Days		4 Days		7 Days	
	P	S	P	S	P	S
3d	—	—	—	+	—	+
5th	—	+	+	+	+	+
7th	+	+	+	+	+	+
9th	+	+	+	+	+	+

* P indicates mycelia cultured from pus. S, mycelia cultured from a stock culture, —, absence of spherules or pus in test animal, and +, presence of spherules in pus from test animal.

and MacNeal and Taylor⁷. Chope approached the problem by injecting the organisms into the testicles of guinea-pigs and killing one animal every four hours. There has been some difference of opinion as to whether the spherules develop from chlamydospores only or whether they may develop also from hyphae that do not contain chlamydospores. Ophuls stated that unless spores are present the fungus is noninfective, but Wohlbach stated that the undifferentiated hyphae are spherulogenic. In order to check this, Chope prepared cultures from infectious pus and from a stock culture and injected them into the testicles of guinea-pigs after two, four and seven days of incubation. The two day cultures contained no evidence of chlamydospores, the four day cultures contained mycelia with early stages of differentiation and the seven day cultures contained moderate numbers of well formed chlamydospores. The results of his test are shown in the accompanying table.

The experiment showed that spherules will form from mycelia which do not contain demonstrable chlamydospores but that it takes longer for them to appear than when mycelium in which chlamydospores are

present is used. Moreover, it indicated also that a two day culture from a stock culture produces spherules more quickly than a two day culture from infectious pus. Whether the undifferentiated mycelia go through the stage of chlamydospore formation after they are injected was not demonstrated.

The sequel of events which occur after the fungus is injected into the testicle is the same as that described by Ophuls^{1b} and by Wohlbach,⁶ differing only in detail. Because experiments had shown that the formation of spherules is more prompt when the mycelia contains mature chlamydospores, the inoculum in our experiments was standardized to the extent that only eight and ten day cultures of mycelium were used, because by this time chlamydospores are well developed. Each culture was examined at intervals microscopically to ascertain the stage of chlamydospore formation before it was injected. The fact that our experiments showed a shorter interval for the completion of the intra-tissue cycle than others that have been reported is undoubtedly due to this feature.

Figure 3 shows the stages through which the chlamydospores pass before they form true spherules and mature by forming endospores. It will be noted that after the injection of the suspension of chlamydospores the outline of the hyphae may be intact on the third day but that the chlamydospores are somewhat rounded and their outer capsule is well defined. At forty-four hours some of these chlamydospores are well rounded out although still connected together as in the hyphae. At sixty hours the spherules are well developed and are as large (about 30 μ) as the immature spherules are likely to be when observed in pus from a patient. By seventy-two hours some of the spherules are filled with endospores, and in ninety-six hours some of them have burst, showing the manner in which the endospores are liberated and how the "envelop" is formed.

On rare occasions we have observed in culture, under anaerobic conditions, spherical enlargements of the chlamydospore segments of the hyphae (fig 3f). In their size and the character of their membrane they resemble the partly matured spherules which may be seen free in pus, but they are not separated from the mycelial growth, and we have never observed any indication of the formation of endospores within them. On only one occasion did we observe a similar type of development in the hyphae of a spherule which had sprouted in pus that had been left standing in an open vessel at room temperature (fig 3g). MacNeal and Taylor⁷ observed one such spherule formation in an anaerobic culture but did not find any in aerobic cultures. During a somewhat limited study of anaerobic cultures we were not able to prove

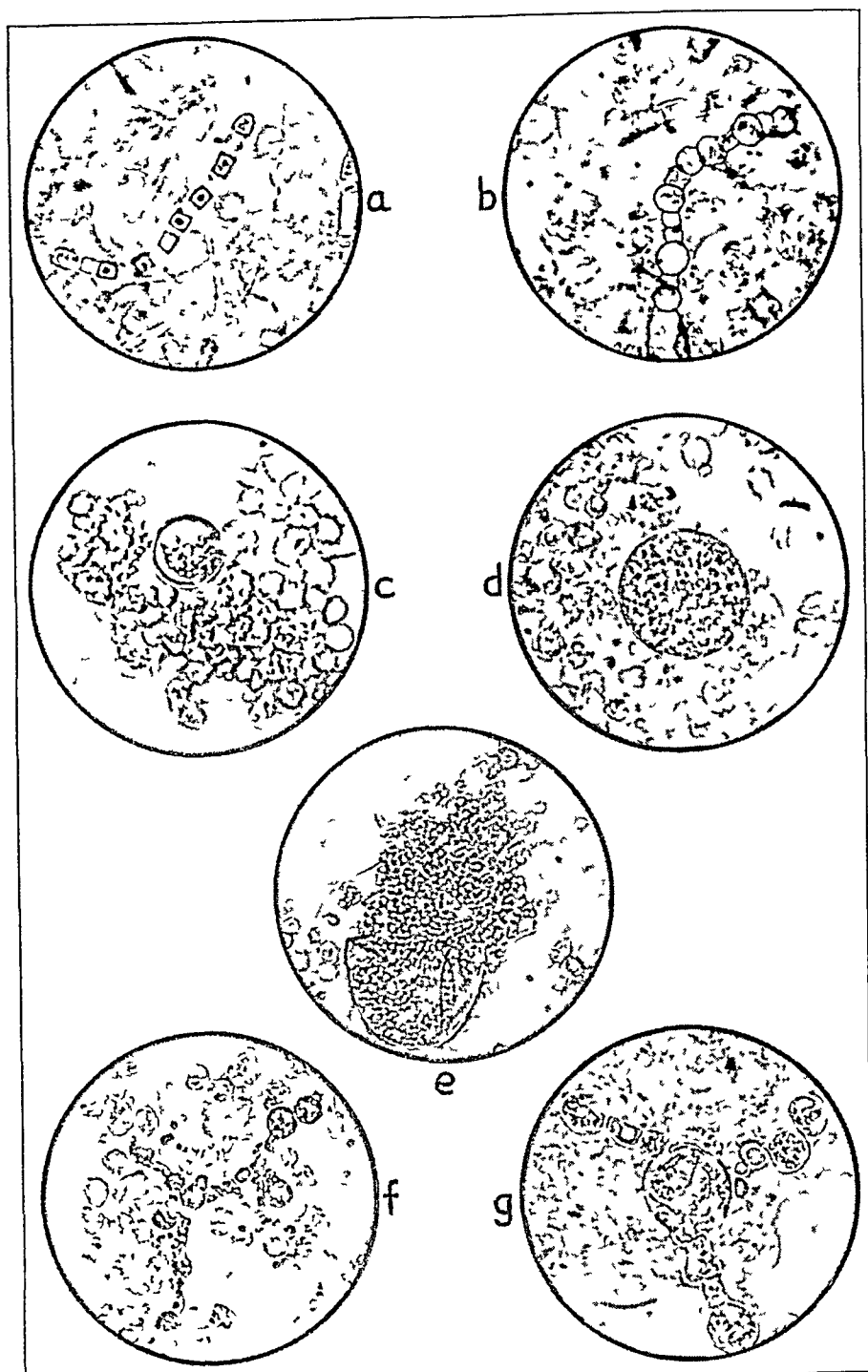


Fig 3—Section *a* shows mycelium in pus with beginning differentiation of the chlamydospores, *b*, mycelium (after forty-four hours) with the chlamydospores having become more circular (retouched), *c*, a single spherule in pus (sixty hours), *d*, a spherule in the stage of endosporulation (seventy-two hours after injection), *e*, ruptured spherule, indicating how the "envelop" is formed and how endospores are liberated (ninety-six hours after injection), *f*, mycelium with small spherical bodies in anaerobic culture, and *g*, mycelium with small spherical bodies in "old" pus which had stood at room temperature

that the formation of spherules depends wholly on the low oxygen tension, because usually no such spherule formation was seen in anaerobic cultures

Occasionally endosporulating spherules with a different appearance are encountered in pus or infected tissues, i. e., the spherules have large central vacuoles and show peripheral arrangement of the endospores. Rixford^{2b} first described these in the report of his second case and said that they might represent a different species of the organism. He suggested the name *Coccidioides pyogenes* and said he believed they represented a more virulent form than *Coccidioides immitis*. Mazzai has described a similar form which was considered to be a new species and to which Fonseca gave the name *Pseudococcidioides Mazzai*. The article describing this form was not available, but de Almeida¹⁷ in discussing it, makes the following quotation

the formation of the spores of *Pseudococcidioides Mazzai* is accomplished by the appearance of radiating openings in the protoplasm which divide the organism (spherule) into cones. Later, new divisions are formed but are parallel to the membrane of the cell. These divisions cut the original cell perpendicularly and determine the appearance of polyhedral cells. Some more fissures develop irregularly, dividing the spores already formed so that they become still smaller and more irregular. Finally these spores become circular.

De Almeida stated that he had found descriptions of similar spherical bodies in the reports of Rixford and Gilchrist^{2b} and Posadas and that he could see no justification for considering that these bodies represent a different species from *C. immitis*.

In our series we have found the usual type of endosporulating spherules and the types just described lying side by side, having developed from the same chlamyospore mixture (fig. 4*a* to *c*). We are unable to say why some of the spherules develop in one way and some in another. However, we are convinced that they do not represent different species of *Coccidioides* but are variations in development due to some unexplained environmental factor.

Another phenomenon that was first described by Posadas¹⁵ and subsequently by Ophuls^{4a} is the development of a cluster of smaller spherules within the capsule of a mother spherule that has not ruptured. Posadas described these as vegetative forms. "The vegetative form begins with the appearance in the protoplasm of the parasite which is going to divide of small clear spherules which slowly become formed into adult endocysts that are retained within the mother cyst." Ophuls disagreed that a different type was indicated and said that they signify very rapid development. "Sometimes, at least in my first case, the

17 de Almeida, F. P. Considerations sur les genres *Coccidioides immitis* et *Pseudococcidioides Mazzai*, *Compt. rend. Soc. de biol.* **110** 137, 1932.

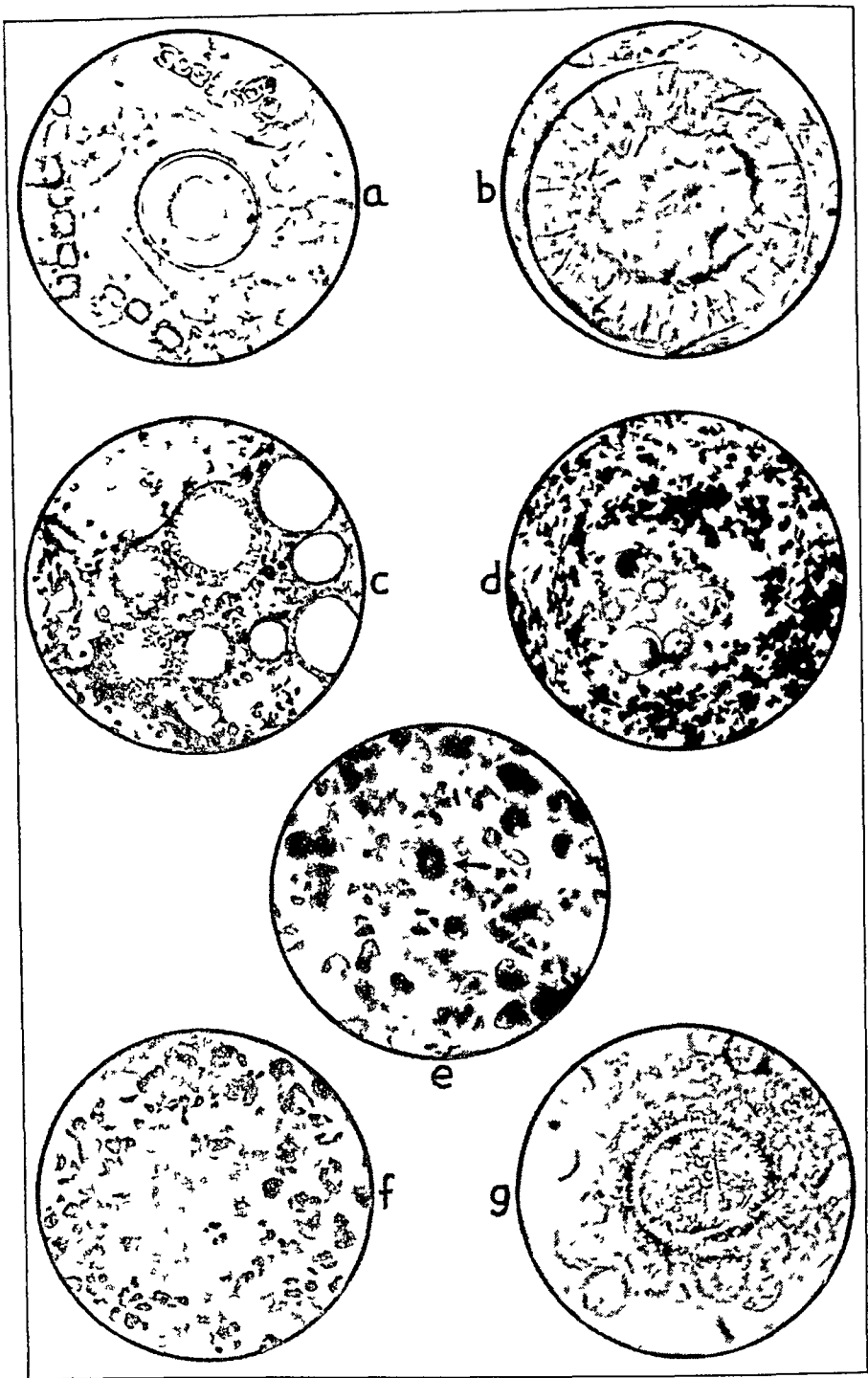


Fig 4—Section *a* shows a vacuolated spherule and the partly differentiated mycelium forty-four hours after injection, *b*, the beginning formation of endospores in a vacuolated spherule (see Mazzai's description), *c*, two types of endosporulation from the same mycelial mixture (the upper one corresponds to Rixford's *C. pyogenes*), *d*, a clump of spherules formed within an unruptured mother spherule, *e*, a minute, burrlike body with fine spicules, found in the depths of a collection of pus, *f*, a fragment of mycelium showing fine spicules, and *g*, a normal-sized spherule with marked prickles formation

development of the young forms from the spores takes place within the old membrane. This seems to occur when the development of the parasite is an especially rapid one. The young forms certainly develop into the larger forms by simple enlargement."

We occasionally have observed such clusters in sections of tissue (fig 4*d*). On occasion we have seen spherules in pus in which the diameter was perhaps double that of the usual size and which were filled with small spherules several times the diameter of the usual endospore. In one series of sections in bovine coccidioid granuloma these clusters were more frequent than we have observed elsewhere, but we have seen them also in the testicle of a guinea-pig eight days after the injection of fungus into the testicle. No explanation for them is apparent.

Another unusual form was first described by Rixford,²¹ who stated that he found prickles on the capsules of a very few of the hundreds of spherules which he examined. Ophuls^{4b} reported that short prickles are almost constant on the outside of sporulating forms, Wohlbach⁶ described them on young spherules developing from mycelia and Ahlfeldt^{8b} stated that they are "found only on the adult forms when they are ready to liberate the young forms."

Our observations coincide more closely with those of Wohlbach. In one series of animals in which intraperitoneal injections were given, abscesses in the epididymis showed minute circular bodies, no larger than an erythrocyte, which were completely surrounded by fine radiating spicules which produced a 'burr-like' appearance (fig 4*e*). These occurred in the depths of collections of pus cells and were not seen elsewhere. In the same sections were seen smooth spherules which did not contain spores but were of average size and were distributed in areas at the edge of the collection of pus cells. These large spherules did not show prickle formation. From our study of tissues, which will be reported later, it is apparent that mature spherules do not usually develop within the dense accumulations of pus but around their margins, so that it may be that these small prickly organisms are the result of an unfavorable environment, due either to insufficient oxygenation or to the toxins which caused the accumulation of the pus.

Prickle formation was observed also in some chains of chlamydo-spores which had not yet separated sixty hours after they were injected (fig 4*f*) and in mature nonsporulating spherules (fig 4*g*), apparently similar forms to those described by Wohlbach. No definite prickle formation was ordinarily observed on endospore-forming spherules, although it was present on rare occasions. Figure 4 shows examples of these various bizarre forms.

The various phases of development of the fungus on culture medium and in the tissues correspond, therefore, on the whole, with those that have been described by previous investigators. They are described here because it seemed advisable to check the various stages of development and to have a clearly cut picture of how the fungus acts, before attempting to ascertain the type of tissue reactions which are caused by it. A study of the manner in which the fungus produces lesions and spreads within the body will be published in a later report.

SUMMARY

Clinical observations are narrated to show that the accepted description of coccidioidal granuloma is that of the advanced or terminal stages of an infection which has not often been recognized during the acute stage.

Proof that primary infection may follow the inhalation of the chlamydospores of *Coccidioides* with the development of bronchopneumonia and erythema nodosum has been given.

A review of the literature concerning the various phases of development of *Coccidioides* in the vegetative form and in the parasitic state has been given, and experimental evidence has been described to aid in evaluating previous work.

This report is preliminary to a description of how this fungus acts within the animal tissue.

SERUM PHOSPHATASE IN JAUNDICE

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AND
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Since Roberts¹ first reported an increase in the phosphatase content of the serum of certain patients with obstructive jaundice, this phenomenon has attracted considerable attention. There still appears to be some difference of opinion regarding the clinical significance of an increase in this factor and its value in differentiating between hepatocellular and obstructive types of jaundice. As this important question can be settled only by the accumulation of observations for large numbers of patients, data obtained for fifty-three patients with jaundice are presented here for the purpose of supplementing those previously reported by other observers.

MATERIAL AND METHODS

The phosphatase content of the serum was determined by the method of Bodansky,² blood being withdrawn after a fasting period of about fourteen hours. In our experience, based on determinations made for hospital patients, values below 7 units for adults and 15 units for children are without clinical significance. In thirty-one of the fifty-three patients studied the jaundice was of extrahepatic origin, some form of malignant growth constituting the underlying basis in eighteen instances. In twenty-two patients the jaundice was dependent on conditions commonly regarded as producing icterus of the hepatocellular variety.

RESULTS

The results obtained are presented in the accompanying tables, which include also simultaneous estimations of the bilirubin content of the serum (van den Bergh), the concentration of cholesterol, the urobilinogen content of the urine (Wallace and Diamond) and the bromsul-

From the Laboratory of Biochemistry, the Jefferson Hospital, and the Department of Medicine, the Jefferson Medical College.

1 Roberts, W. M. Variations in the Phosphatase Activity of the Blood in Disease, *Brit J Exper Path* **11** 90, 1930, Blood Phosphatase and the van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, *Brit M J* **1** 734, 1933.

2 Bodansky, A. Phosphatase Studies. II. Determination of Serum Phosphatase, Factors Influencing the Accuracy of the Determination, *J Biol Chem* **101** 93, 1933.

phalein retention (thirty minutes after the administration of 2 mg per kilogram of body weight)

Table 1 comprises thirty-six serum phosphatase determinations for thirty-one patients with obstructive jaundice. All were adults, with the exception of patient 19, an infant of 3 months with congenital obliteration of the bile ducts. The bilirubin concentration of the serum

TABLE 1—*Serum Phosphatase Values for Patients with Obstructive Jaundice*

Patient Number	Age	Serum Bilirubin, Mg per 100 Cc	Bromsul phalein, %	Phosphatase, Units	Urobilinogen, Urine Dilution	Plasma Cholesterol, Mg per 100 Cc	Diagnosis
1	59	39.0 36.0	100 100	23.4 24.6	Negative	243	Carcinoma of pancreas
2	63	26.0	100	26.0	Negative	263	Carcinoma of pancreas
3	41	26.0 10.0	100 100	12.3 10.2	1 10	281	Stone in common duct
4	42	26.0	100	16.0	Negative	392	Stone in common duct
5	52	24.0	60	21.1	Negative	396	Carcinoma of pancreas
6	58	21.0	100	8.4	Negative	238	Carcinoma of pancreas
7	58	21.0	40	18.1	Negative	206	Carcinoma of pancreas
8	39	7.5 19.5	80	14.0 10.0	1 10 Negative	470	Carcinoma of pancreas
9	36	15.2 9.0	100 70	11.0 17.9	Negative Negative	1,103 300	Stricture of common duct
10	44	13.2	80	56.7	1 10	196	Carcinoma of pancreas
11	65	12.0	80	9.8	Negative	376	Stone in common duct
12	52	11.5	50	8.6	1 20	194	Stone in common duct
13	56	11.5	100	20.6	Negative	241	Carcinoma of liver
14	54	11.2	80	8.7	Negative		Carcinoma of ampulla
15	57	10.7	60	7.0	Negative	256	Carcinoma of pancreas
16	29	10.4	100	21.3	Negative	264	Stricture of common duct
17	70	10.2	100	23.7	Negative	192	Stone in common duct
18	53	10.0	100	6.2	1 40	232	Carcinoma of pancreas
19	3 mo	18.3	100	7.2	Negative	340	Congenital obliteration of bile ducts
20	39	7.4	50	21.3	1 40	570	Carcinoma of pancreas
21	32	7.3	80	20.5		248	Stone in common duct
22	45	7.2 9.6	40 80	24.7 22.1	1 10 Negative	548	Carcinoma of liver
23	60	6.9	20	8.4	1 100	302	Carcinoma of pancreas
24	49	6.4	100	35.0	Negative	408	Carcinoma of pancreas
25	27	6.4	10	11.1	1 10	168	Lymphosarcoma
26	55	6.4	80	24.7	Negative	135	Stone in common duct
27	73	5.4	50	10.6	1 10		Pancreatitis
28	73	4.8	80	17.1	1 10		Carcinoma of pancreas
29	60	4.5	50	9.2	1 20		Carcinoma of pancreas
30	50	4.4	100	7.9	1 10	232	Stone in common duct
31	56	2.2	60	10.9	1 20	241	Stone in common duct

ranged from 2.2 to 39 mg per hundred cubic centimeters and the phosphatase content from 6.2 to 56.7 units per hundred cubic centimeters.

Table 2 comprises twenty-four phosphatase determinations for 22 patients with jaundice of hepatocellular origin. The bilirubin concentration of the serum ranged from 0.6 to 13.8 mg and the phosphatase content from 4.9 to 24.5 units per hundred cubic centimeters.

The data presented in table 3 indicate the distribution of the phosphatase values for the two groups of patients. The patients with obstructive jaundice are divided into two groups, because of the report

by some observers of an increase in phosphatase activity in association with malignant neoplastic disease and because of the usually progressive and persistent character of the jaundice in such cases as contrasted with jaundice due to calculous obstruction of the common duct

TABLE 2—*Serum Phosphatase in Hepatocellular Jaundice*

Patient Number	Age	Serum Bilirubin, Mg per 100 Cc	Bromsul phalein, %	Phos phatase, Units	Urobili nogen Urine Dilution	Plasma Cholesterol, Mg per 100 Cc	Diagnosis
32	69	13.8	100	4.9			
		1.5	60	6.8	1:60	115	Cholecystitis
		0.6	15	5.8			
33	26	13.5	20	11.5	1:40	122	Catarrhal jaundice
34	34	11.4	100	14.9	1:100	156	Cholecystitis
35	30	10.4	80	21.0	1:200	102	Arsphenamine hepatitis
36	48	9.8	100	9.9	1:40	245	Arsphenamine hepatitis
37	48	9.8	90	6.8	1:100	104	Portal cirrhosis
38	22	8.8	80	8.7	1:400	90	Catarrhal jaundice
39	18	8.7	30	7.0	1:100	95	Banti's disease
40	34	8.2	100	12.0	1:200	98	Catarrhal jaundice
41	14	7.2	80	12.3	1:200	110	Catarrhal jaundice
42	40	7.2	30	5.4	1:100	140	Cholecystitis
43	59	7.1	50	6.4	1:80	146	Carcinoma of liver, no obstruction
44	14	6.9	30	23.2	1:100	224	Splenic anemia
45	34	6.8	80	5.2	1:100	130	Hepatitis
46	57	5.8	100	12.2	1:100	100	Hepatitis
47	25	5.6	69	9.4	1:40	162	Cholecystitis
48	35	4.8	80	9.4	1:200	128	Catarrhal jaundice
49	56	4.8	60	15.2	1:80	142	Portal cirrhosis
50	67	4.2	15	12.6	1:20	184	Syphilis of liver
51	69	3.8	15	7.2	1:60	192	Cholecystitis
52	59	1.5	90	24.5	1:200	105	Cholecystitis
53	24	1.4	20	7.9	1:40	117	Hepatitis

TABLE 3—*Distribution of Phosphatase Values for Thirty-One Patients with Obstructive and Twenty-Two Patients with Hepatocellular Jaundice*

	Number of Values Falling Within the Range			
	0 to 10 Units	10 to 20 Units	20 to 30 Units	Over 30 Units
Nonmalignant obstruction	4	4	5	0
Malignant obstruction	6	4	6	2
Total obstruction	10	8	11	2
Hepatocellular jaundice	12	7	3	0

COMMENT

These data are essentially in agreement with those reported by Bodansky and Jaffe,³ Herbert,⁴ and Greene, Shattuck and Kaplowitz⁵

3 Bodansky, A, and Jaffe, H. L. (a) Phosphatase Studies. IV. Serum Phosphatase of Non-Osseous Origin, Significance of the Variations of Serum Phosphatase in Jaundice, *Proc Soc Exper Biol & Med* **31** 107, 1933, (b) Phosphatase Studies. VIII. Increase of Serum Phosphatase After Bile Duct Ligation in Dog, *ibid* **31** 1179, 1934

4 Herbert, F. K. Plasma Phosphatase in the Various Types of Jaundice, *Brit J Exper Path* **16** 365, 1935

5 Greene, C. H., Shattuck, H. F., and Kaplowitz, L. The Phosphatase Content of the Blood Serum in Jaundice, *J Clin Investigation* **13** 1079, 1934

As in the case of the data presented by Greene and his colleagues, the phosphatase values obtained in the present series exhibit a wide overlapping in obstructive and hepatocellular jaundice. This observation is contradictory to the findings of Roberts¹ and Rothman, Meranze and Meranze,⁶ who said they believed that there is a rather sharp line of demarcation in this regard between these two types of jaundice. Rothman and his associates found values greater than 10 units per hundred cubic centimeters (modified Roberts method) for twenty-five of twenty-nine patients with obstructive jaundice and 10 units or less for eighteen of twenty-four with hepatocellular jaundice. Although the data reported by practically all investigators of this problem indicate that a larger proportion of patients with obstructive than of those with hepatocellular jaundice exhibit very high phosphatase values, it appears that the

TABLE 4—*Distribution of Phosphatase Values for Fifty Patients with Obstructive and Forty-One with Hepatocellular Jaundice (Combined Data of Present Series and That of Greene, Shattuck and Kaplowitz)*

	Number of Values Falling Within the Range			
	0 to 10 Units	10 to 20 Units	20 to 30 Units	Over 30 Units
Nonmalignant obstruction	5	10	6	4
Malignant obstruction	7	5	9	4
Total obstruction	12	15	15	8
Hepatocellular jaundice	15	16	7	3

relatively sharp delimitation of these values in the groups of patients studied by Roberts¹ and Rothman, Meranze and Meranze⁶ is purely coincidental. Unfortunately the difference in the methods employed by different observers renders impossible a quantitative correlation of all the reported observations.

Table 4 comprises the combined data of the present series and that of Greene, Shattuck and Kaplowitz⁵ obtained by the same method (Bodansky). Comparison with table 3 indicates clearly the alteration in distribution of phosphatase values when the influence of chance is lessened by increasing the number of observations. It is noted that the value for serum phosphatase was below 10 units in 24 per cent of fifty patients with obstructive and in 36.6 per cent of forty-one with hepatocellular jaundice. In view of this fact, the observation that values above 20 units were obtained in 46 per cent of those with obstructive jaundice and in only 24.4 per cent of those with hepatocellular jaundice has little if any practical significance from the standpoint of differential diagnosis.

6 Rothman, M. M., Meranze, D. R., and Meranze, T. Blood Phosphatase as an Aid in the Differential Diagnosis of Jaundice, *Am. J. M. Sc.* **192**: 526, 1936.

As has been found by previous investigators, there was no close correlation between the degree of bilirubinemia and the phosphatase level for either group of patients. This lack of relationship is well illustrated by patients 6, 19, 20, 22, 24, 26, 32 and 52. It is interesting in this connection to note that for a patient with portal cirrhosis studied by Greene and his associates⁵ the bilirubin content of the serum was 30.5 mg per hundred cubic centimeters and the phosphatase content was 1.3 units, whereas for another the phosphatase content was 19.9 units and the bilirubin content was within normal limits.

In the cases reported by Herbert,⁴ although there was no close correlation between the duration of jaundice and the level of serum phosphatase, very high values were more frequent in cases of malignant growth than in cases of calculous obstruction. It was suggested that recent, incomplete or intermittent obstruction may be associated with relatively slight increases in the phosphatase content. However, when our data are combined with those of Greene, Shattuck and Kaplowitz,⁵ there appears to be little significant difference in distribution for patients with malignant and those with nonmalignant obstructive jaundice. Furthermore, the serum phosphatase was normal in patient 19, an infant of 3 months with congenital obliteration of the bile ducts. These observations appear to indicate the lack of influence of duration and permanence of obstruction in this connection. However, it must be borne in mind that, as pointed out by Bodansky and Jaffe,^{3a} anemia, malnutrition and senility tend to lower the phosphatase content of the serum and should be taken into consideration in interpreting clinical variations in this factor.

It seems futile in the present state of knowledge to theorize regarding the possible mechanism of production of the increase in serum phosphatase in jaundice of obstructive and hepatocellular origin. The subject has been reviewed recently by Herbert⁴ and one of us (A. C.).⁷ It appears to be clear, however, that this increase cannot be explained, as Herbert implied, on the basis of obstruction to the flow of bile, either extrahepatic or intrahepatic. This hypothesis is contradicted by observations, such as those of Greene and his colleagues⁵ in portal cirrhosis, just cited, and by the data for patient 52 in the present series, which showed marked elevation of the phosphatase level accompanied with little or no increase in serum bilirubin. The presence of normal phosphatase activity in an infant of 3 months with congenital obliteration of the bile ducts appears to be incompatible with such a hypothesis. Further-

⁷ Cantarow, A. Review of Phosphatase Activity and Calcium and Electrolyte Metabolism, *Internat. Clin.* **1**: 230, 1936.

more, Stewart, McCool and one of us (A C)⁸ found little or no increase in the phosphatase content in a large series of cats with total biliary stasis of varying duration produced by ligation of the common bile duct. This observation is interesting because of the marked increase which was noted under such circumstances in dogs by Bodansky and Jaffe^{3b} and Armstrong and King.⁹ It seems unlikely that there would be so marked a species difference in this respect if stasis per se were the only etiologic factor of fundamental importance. It should be noted also that Hartman and Schelling¹⁰ and Armstrong and King⁹ found an increase in serum phosphatase in dogs in the presence of hepatic functional impairment produced by a variety of methods (modified Eck fistula, high voltage roentgen irradiation, carbon tetrachloride, chloroform, phosphorus and toluylenediamine).

The data obtained for the present series of patients support the view that determination of the level of serum phosphatase is of no value in distinguishing jaundice of obstructive from that of hepatocellular origin.

SUMMARY

Serum phosphatase determinations were obtained for thirty-one patients with obstructive and twenty-two with hepatocellular jaundice. There was a wide overlapping of phosphatase values in the two groups which became even more pronounced when the present data were combined with those reported by other observers employing the same methods. It appears that this procedure is of no value in differentiating between these two types of jaundice.

8 Cantarow, A., Stewart, H. L., and McCool, S. G. Serum Phosphatase in Cats with Total Bile Stasis, *Proc Soc Exper Biol & Med* **35** 87 (Oct) 1936.

9 Armstrong, A. R., and King, E. J. Serum Phosphatase in Toxic and Haemolytic Jaundice, *Canad M A J* **32** 379, 1935.

10 Hartman, F. W., and Schelling, V. Serum Phosphatase in Experimental Insufficiency of the Liver, *Arch Path* **18** 594 (Oct) 1934.

Progress in Internal Medicine

BLOOD

A REVIEW OF THE RECENT LITERATURE

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PERNICIOUS ANEMIA

ETIOLOGY

The mechanism of the development of pernicious anemia has been explained by Castle¹ on the basis of interaction of an "intrinsic factor" secreted by the gastric mucosa and an "extrinsic factor" provided by the diet, thereby producing a substance which controls the maturation of red blood cells in the bone marrow Greenspon² has performed experiments which in his opinion suggest a different interpretation of the observations of Castle Greenspon's theory is as follows It is assumed that an erythrocyte-stimulating hormone is secreted by the gastric mucosa When pernicious anemia develops there is a loss of this hormone, coincident with atrophy of the gastric glands, and the anemia of the disease develops In support of his theory this investigator reported that the injection of extracts of gastric mucosa of the hog into rabbits and guinea-pigs caused (1) a substantial increase in the number of circulating erythrocytes, (2) moderate reticulocytosis and (3) hyperplasia of the bone marrow Certain other experiments were performed which led to the conclusion that the addition of pepsin destroys the antianemic properties of stomach U S P In addition, the author

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The present review deals with the literature on hematology which appeared in 1936 A few articles which were published in 1935 are included To conserve space it has been necessary to select certain papers at the expense of others A number of the more important contributions which have been omitted will be included in subsequent reviews

1 Castle, W B The Etiology of Pernicious and Related Macrocytic Anemias, *Science* **82**:159 (Aug 23) 1935

2 Greenspon, E A The Nature of the Antipernicious Anemia Principle in Stomach Method to Improve Stomach Preparations, *J A M A* **106** 266 (Jan 25) 1936

concluded that the oral administration of gastric juice alone is effective if peptic activity is prevented. This is contrary to the basic experiments of Castle and his co-workers. Greenspon's theory, which places a different interpretation on the experiments of Castle relating to the interaction of an intrinsic factor and beef muscle (extrinsic factor), may be stated as follows. Normal gastric juice contains an antianemic factor and free pepsin. The pepsin has an "antagonistic" action toward the antianemic factor and renders it inert. When gastric juice is incubated with beef muscle, the protein of the muscle interacts with the free pepsin to form bound pepsin, thereby permitting the antianemic factor to become active. From the experiments performed and certain theoretical considerations, a new method of making stomach preparations was suggested in which the antagonistic action of pepsin was eliminated.

Hanes, Hansen-Pruss and Edwards³ repeated some of Greenspon's experiments, adhering strictly to his technic, with negative results. Greenspon had reported that "the oral administration of normal gastric juice is effective in pernicious anemia if peptic activity is prevented, also that the mere physical presence of pepsin is not destructive to the anti-pernicious factor, if the pepsin is inactive." Hanes and his colleagues fed gastric juice, modified by the technic of Greenspon, to 5 patients with pernicious anemia and did not observe any subjective or objective evidence of improvement in the condition of the patients. Other experimental data which are not in accord with Greenspon's theory have been reported by Flood and West,⁴ Ungley⁵ and Moffett and Fitz-Hugh and Creskoff.⁶

Castle and Ham⁷ in a direct reply to Greenspon cited a group of experiments which "fail to sustain" Greenspon's conclusion. Their observations led to the following conclusions:

1 Normal human gastric juice does not contain, on oral administration, an "antipernicious anemia principle" effective without contact with food (extrinsic factor).

3 Hanes, F. M., Hansen-Pruss, O. C., and Edwards, J. W. The Feeding of Modified Gastric Juice in Pernicious Anemia, *J. A. M. A.* **106** 2058 (June 13) 1936.

4 Flood, C. A., and West, R. Some Properties of Castle's Intrinsic Factor, *Proc. Soc. Exper. Biol. & Med.* **34** 542, 1936.

5 Ungley, C. C. Observations on Castle's Intrinsic Factor in Pernicious Anaemia, *Lancet* **1** 1232 (May 30) 1936.

6 Fitz-Hugh, T., Jr., and Creskoff, A. J. Experiments with "Depepsinized" Human Gastric Juice in Treatment of Pernicious Anemia, *Am. J. M. Sc.* **192** 168, 1936.

7 Castle, W. B., and Ham, T. H. Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia. Further Evidence for the Essential Participation of Extrinsic Factor in Hematopoietic Responses to Mixtures of Beef Muscle and Gastric Juice and to Hog Stomach Mucosa, *J. A. M. A.* **107** 1456 (Oct. 31) 1936.

2 Mucosa of hog stomach contains both a thermostable (extrinsic) factor and a thermolabile (intrinsic) factor presumably responsible for the activity of such mucosa and of whole desiccated hog stomach

3 Incubation of normal human gastric juice for two hours at 37.5 C in the presence of native pepsin and hydrochloric acid inactivates only a portion of its content of intrinsic factor.

4 Beef muscle (extrinsic factor) and gastric juice (intrinsic factor) administered without opportunity for contact are not effective in pernicious anemia

Ever since liver therapy has been used in the treatment of pernicious anemia, attempts have been made by various investigators to isolate the active antianemic principle from that substance. In 1935 Dakin and West described the preparation and partial purification of a product from liver which was effective in causing regeneration of blood in pernicious anemia. In 1936 Dakin, Ungley and West⁸ reported further studies on the isolation of this substance and recorded certain conclusions which may be deduced from the chemical data thus acquired. They confirmed their previous observation that the active principle in liver is, or is associated with, a peptide which possesses some of the properties of an albumose. Additional studies indicated that an aminohexose (dextrosamine) is not an essential part of the molecule. On hydrolysis the peptide yields arginine, leucine, amino-acetic acid, proline, hydroxyproline, aspartic acid and an acid resembling hydroxyglutamic acid. Their work indicated that the substance has a molecular size of about 2.1 millimicrons and a molecular weight between 2,000 and 5,000. When the methods of isolating this material are applied to kidney and brain, they do not yield a hematopoietic substance.

Of interest from the standpoint of the relation of gastric juice to the etiology of pernicious anemia are the experiments of Mermod.⁹ This investigator, following the method of Jacobson,¹⁰ demonstrated that an increase in the number of reticulocytes in the peripheral blood of guinea-pigs followed the intraperitoneal injection of congo red and the intravenous injection of gastric juice from normal subjects and those having gastric anacidity but no anemia. The intramuscular injection of gastric juice from patients with pernicious anemia was not followed by an increase in the reticulocyte count of guinea-pigs within

8 Dakin, H. D., Ungley, C. C., and West, R. Further Observations on the Chemical Nature of a Hematopoietic Substance Occurring in Liver, *J. Biol. Chem.* **115** 771, 1936

9 Mermod, C. Reticulocytosis in Guinea Pig Following Injections of Gastric Juice and Congo Red, *J. Clin. Investigation* **15** 559, 1936

10 Jacobson, B. M. Note on Guinea-Pig Method of Assay of Liver Extract, *Brit. J. Exper. Path.* **17** 307, 1936

the first eight days. The reaction of the guinea-pig to the intramuscular injection of gastric juice was proposed as a test for the diagnosis of anemia of obscure origin. Such data could be interpreted as further evidence that the fundamental defect in pernicious anemia is in the gastric secretions. The failure of Jacobson's method of studying reticulocytogenic substances to receive unanimous confirmation causes one to withhold complete acceptance of Mermod's work until additional studies have been made.

Cheney¹¹ incubated scrapings of human duodenal mucosa with liver and liver extract and administered the resultant substance to patients with pernicious anemia and other macrocytic anemias. He concluded that a "duodenal ferment" increases the efficacy of liver as a therapeutic agent in these types of anemia. He considered that the "unknown ferment" ("intrinsic factor" of Castle) is at a higher concentration in the duodenal mucosa than in the stomach and that in patients with pernicious anemia there is a gastroduodenal defect or an inactivity of the pyloric region (Brunner's gland). He suggested that the activity of the duodenal mucosa explains the absence of macrocytic anemia in some patients with gastric achylia and atrophy of the mucosa of the stomach and also may account for the failure of this type of anemia to follow gastrectomy in all instances.

Goldhamer¹² studied the volume of gastric juice of 26 patients during a relapse of pernicious anemia. The average volume secreted per hour was 20 cc, as compared with the normal secretion, which is about 150 cc per hour. When this material was incubated with beefsteak and fed to other patients during a relapse, a reticulocyte response was observed. It was concluded from these experiments that in patients with pernicious anemia the intrinsic factor was present in the stomach contents but that the deficiency was quantitative rather than qualitative. Palmer and Porter¹³ and Fitz-Hugh and Creskoff⁶ performed similar experiments but were unable to confirm this work.

The relationship of the functions of the stomach to the production of red blood cells is not limited to pernicious anemia. Naegeli¹⁴ pointed out that many anemias may result from deficiencies of the stomach and gastro-intestinal tract but that liver and desiccated stomach are of value

11 Cheney, G. Investigation into Production of Proteolytic Ferment in Duodenum Which Will Increase Anti-Anemic Efficacy of Liver. Its Relationship to Cause of Pernicious Anemia, *Am J Digest Dis & Nutrition* **3** 541, 1936.

12 Goldhamer, S. M. Presence of Intrinsic Factor of Castle in Gastric Juice of Patients with Pernicious Anemia, *Am J M Sc* **191** 405, 1936.

13 Palmer, W. L., and Porter, R. T. Combined Cord Degeneration Without Anemia. A Case Report with Studies Bearing on the "Intrinsic Factor" of Castle, *J Clin Investigation* **15** 343, 1936.

14 Naegeli, O. Die Beziehungen des Magen-Darmkanals zur Blutbildung und zur Entstehung von Anamien, *Helvet med acta* **3** 581, 1936.

only in pernicious anemia. It is shown by Apperly and Cary¹⁵ that there is a direct relationship between the red cell count of peripheral blood and the degree of gastric acidity. In anemia due to hemorrhage, if more than one third of the total red blood cells are lost "free" acid disappears from the stomach content. As the blood approaches normal, the "free acid" returns, and the amount gradually approaches normal. In polycythemia the acidity again falls. The latter observation is contrary to the beliefs of some investigators, who are of the opinion that the increased production of red blood cells in polycythemia is the result of overactivity of gastric secretion. Apperly¹⁶ pointed out that when anemia is associated with achlorhydria, it is necessary to distinguish between "achlorhydric" anemia and the absence of "free" acid as a result of a reduced number of red cells in the peripheral blood.

In studying the anemias of children Racugno¹⁷ stated that many of them can be differentiated by careful studies of the gastric chemistry. In his opinion the gastric changes are secondary to the existing anemia.

Several interesting observations were reported by Karczag,¹⁸ who made spectrographic studies of the gastric contents of patients with pernicious anemia. He pointed out that the gastric secretions have a selective absorption spectrum and that the values obtained for patients with pernicious anemia are quantitatively lower but similar in type to those of normal persons. The gastric juice is not a protein, polypeptide, aromatic amino-acid, lactic acid or bile pigment but resembles the vitamin B complex.

SYMPTOMATOLOGY, CHANGES IN THE BLOOD AND MANIFESTATIONS DUE TO LESIONS IN THE SPINAL CORD AND BRAIN

An analysis of 580 consecutive cases of true pernicious anemia was reported by Isaacs¹⁹. From the data a patient with pernicious anemia is defined statistically as a man or woman (equal possibility) between the ages of 35 and 55 years, of no specific nationality but generally of a race originating in the northern European countries, who is underweight, who has light-colored hair, generally blue eyes and pale skin, and long wide ears, and who shows no secretion of hydrochloric acid.

15 Apperly, F. L., and Cary, M. K. Relation of Gastric Acidity to Erythrocyte Content of Blood, *Am J Digest Dis & Nutrition* **3** 466, 1936.

16 Apperly, F. L. Gastric Acidity and Its Significance. Clinical and Experimental Study, *Lancet* **1** 5 (Jan 4) 1936.

17 Racugno, A. Osservazioni intorno alle conoscenze sul chimismo gastrico nei bambini, *Clin pediat* **18** 129 and 331, 1936.

18 Karczag, L. The Spectrographic Anomalies of Gastric Juice in Pernicious Anaemia, *Lancet* **1** 947 (April 25) 1936.

19 Isaacs, R. Blood Cell Morphology in Constitutional Types and Heredity, in *Medical Papers Dedicated to H. A. Christian, Physician and Teacher, in Honor of His Sixtieth Birthday*, Baltimore, Waverly Press, Inc., 1936, p. 538.

at any time in the stomach, relative hypotension, a tendency to hyperchromic macrocytic anemia, leukopenia and hyperbilirubinemia, atrophy of the lingual papillae, and neurologic changes associated with lesions in the posterolateral columns of the spinal cord

In Hoffmann's²⁰ series of 57 patients the total number of leukocytes varied from 2,000 to 3,500 per cubic millimeter. There was an initial increase after liver therapy or blood transfusion. In half the patients who received liver therapy the improvement in the leukocyte picture did not appear until after there was a response of the red blood cells, after which the "shift to the right" of the polymorphonuclears, the relative lymphocytosis and the monocytopenia were replaced by a more normal condition. Eosinophilia, however, frequently persisted. In half the cases the rapid improvement in the leukocyte picture was of prognostic value.

Reichel²¹ noted that the speed of sedimentation of the red blood corpuscles is increased when the anemia is marked and that it decreases as the blood count improves.

Van der Sande²² described a condition noted by others, namely, the development of carcinoma of the stomach in patients with pernicious anemia. The patients fall into the proper age group and would naturally be susceptible to the development of a neoplasm. So far no definite relationship between the two diseases has been established. It is wise to think of the possibility of a gastric neoplasm in patients under treatment for pernicious anemia. Among diseases and syndromes which have been described in association with pernicious anemia are hyperthyroidism (Andrus and Wintrobe²³), diabetes mellitus, terminating in acute myeloid leukemia (Elman and Marshall²⁴), myxedema (Holbøll²⁵ and Greene²⁶), and bacillary dysentery (Greene²⁷).

20 Hoffmann, D. Beobachtungen über das Verhalten des weissen Blutbildes bei perniziöser Anämie in der Zeit vor und nach Einführung der Lebertherapie, *Klin Wchnschr* **15** 598 (April 25) 1936.

21 Reichel, H. Blutkörperchensenkung bei perniziöser Anämie, *Klin Wchnschr* **14** 1679 (Nov 23) 1935.

22 van der Sande, D. Question of Relation Between Pernicious Anemia and Gastric Cancer, *Nederl tijdschr v geneesk* **80** 4774 (Oct 24) 1936.

23 Andrus, E. C., and Wintrobe, M. M. Note upon the Association of Hyperthyroidism and Pernicious Anaemia, *Bull Johns Hopkins Hosp* **59** 291, 1936.

24 Elman, C., and Marshall, S. Anaemia of Pernicious Type Complicated by Diabetes Mellitus and Terminating in Acute Myeloid Leukaemia, *Lancet* **2** 1094 (Nov 7) 1936.

25 Holbøll, S. A. Anaemia perniciosa og myxødem, *Hospitaltid* **78** 1181 (Nov 12) 1935.

26 Greene, J. A. Comparison of Symptoms, Physical and Laboratory Findings of Myxedema and Pernicious Anemia, with Report of Three Cases, *Ann Int Med* **10** 622, 1936.

27 Greene, J. A. Diagnosis of Bacillary Dysentery. Report of a Chronic Case Associated with Pernicious Anemia, *J Iowa M Soc* **26** 148, 1936.

Patients with pernicious anemia may first present themselves to the physician for relief of the neurologic symptoms. Of Craig's²⁸ series, 12.7 per cent of the patients with pernicious anemia had a neurologic complication as the main symptom: paresthesias, 80 per cent, girdle pain, 2.8 per cent, and sensation of a tight band around the knees, 1.7 per cent. In 1.4 per cent of the patients the nervous manifestations antedated the appearance of the anemia. Among other authors reporting carcinoma of the stomach and pernicious anemia are Calabresi,²⁹ Greyman, Livshits and Pevzner,³⁰ Grill,³¹ Rambach,³² Silverman,³³ and Thiele.³⁴

The extremely common occurrence of symptoms and signs referable to the central nervous system in pernicious anemia has led most investigators to the conclusion that it is a part of the same disease process. The opinion has been expressed that if neurologic complications are absent in a case of macrocytic anemia, although pernicious anemia is a possibility, one should look for other causes of macrocytic anemia. The etiology of the changes in the nervous system remains obscure. It is believed by some that the manifestations in the spinal cord may result from a vitamin deficiency. Others still maintain that there is a specific neurotoxin due to a disturbance in lipid metabolism or that the changes in the central nervous system are related directly to the anemia. There is considerable opposition to the latter view. Palmer and Porter¹³ have reported a case of combined degeneration of the spinal cord without any evidence of anemia.

The most common neurologic symptoms are numbness and tingling of the extremities, coldness, ataxia, loss of finer coordination of the fingers and disturbances of the bowel and bladder. The character of the signs depends on the site of the lesion and the extent of the patho-

28 Craig, W. M. Tumors of the Spinal Cord and Their Relation to Medicine and Surgery, *J. A. M. A.* **107** 184 (July 18) 1936.

29 Calabresi, M. Anemia perniciosa e carcinoma gastrico, *Policlinico (sez. prat.)* **43** 1685 (Sept. 21) 1936.

30 Greyman, A. A., Livshits, S. M., and Pevzner, S. D. Malignant Degeneration of Gastric Adenoma Associated with Pernicious Anemia, *Vestnik khir.* **45** 245, 1936.

31 Grill, H. Ein Fall von Anaemia perniciosa und Magencarcinom, *Folia haemat.* **54** 410, 1936.

32 Rambach, H. Ueber die Entwicklung von Magenkrebs bei der perniziösen Anämie, *Monatschr. f. Krebsbekämpfung* **4** 201, 1936.

33 Silverman, S. Pernicious Anaemia Followed by Carcinoma of the Stomach, *Lancet* **2** 71 (July 11) 1936.

34 Thiele, W. Perniziöse Anämie und Magencarcinom unter besonderer Berücksichtigung ihres familiären Auftretens, *Klin. Wchnschr.* **15** 921 (June 27) 1936.

logic involvement of the spinal cord Tournelles and Vazquez³⁵ pointed out that the anterior, lateral or posterior gray columns of the cord may be involved separately or simultaneously As a result the reflexes may be increased, decreased or absent The mental picture is not specific, and many observers are of the opinion that the manifestations of cerebral involvement are independent of the disease process of pernicious anemia Schwab and Schwab³⁶ discussed the association of pernicious anemia and the parkinsonian syndrome and discussed the possible etiology

The neurologic and psychiatric features have been emphasized by Cain and Ceillier,³⁷ Cain, Ceillier, Cattani and Bachman,³⁸ Langeluddeke,³⁹ and Petit and Delmond⁴⁰

TREATMENT

After the use of liver extract made by the method of Dakin and West, improvement in the blood of patients with pernicious anemia was noted by Ungley, Davidson and Wayne⁴¹ and also by Wilkinson⁴² In 11 patients doses of from 1 to 6 cc (100 to 600 mg) caused an increase in the red blood cell count in forty days, but larger doses were required for the production of red blood cells at a maximal rate The results demonstrate that the Remcke acid extraction of liver separates a considerable amount of the hematopoietically active principle

Murphy⁴³ recommended the intramuscular injection of liver extract as the method of choice in the treatment of pernicious anemia He

35 Tournelles, J F, and Vazquez, P C Neuro-Anemic Syndrome of Unusual Localization, *Semana med* **2** 1583 (Dec 3) 1936

36 Schwab, S I, and Schwab, R S Pernicious Anemia and Combined System Disease with Diabetes Mellitus and Parkinsonian Syndrome Report of Case, *Arch Neurol & Psychiat* **35** 126 (Jan) 1936

37 Cain, A, and Ceillier, A Contribution à l'étude des psychoanémies Examen psychiatrique de quatre cas d'anémie de Biermer, *Ann méd-psychol* (pt 1) **94** 582, 1936

38 Cain, A, Ceillier, A, Cattani, R, and Bachman Anémie biermérienne et troubles psychiques, *Sang* **10** 770, 1936

39 Langeluddeke, A Ein Fall von perniziöser Anämie mit Psychose und anderen selteneren Symptomen, *Deutsche med Wchnschr* **62** 963 (June 12) 1936

40 Petit, G, and Delmond, J Le syndrome d'Adie en pathologie mentale Ses rapports avec les syndromes neuro-et psychoanémiques, *Ann méd-psychol* (pt 1) **94** 497, 1936

41 Ungley, C C, Davidson, L S P, and Wayne, E J Treatment of Pernicious Anaemia with Dakin and West's Liver Fraction (Anahaemin), *Lancet* **1** 349 (Feb 15) 1936

42 Wilkinson, J F Note on Anti-Anaemic Principle of Liver, *Lancet* **1** 354 (Feb 15) 1936

43 Murphy, W P Treatment of Pernicious Anemia with Intramuscular Injections of Highly Concentrated Solution of Liver Extract, *Am J M Sc* **191** 597, 1936

used a preparation in which 1 cc was made from 100 Gm of liver. Injections from every ten to twenty-eight days served to maintain the blood at a normal level.

Autolyzed liver extract was found to be effective by Klumpp⁴⁴ in doses of from 1 to 8 teaspoonfuls daily (average 3 teaspoonfuls), representing from 150 to 200 Gm of liver.

Instead of from 30 to 50 Gm of dried stomach, Henning and Keilhack⁴⁵ used 5 Gm of a powder made from the mucous membranes of the antrum. For the "extrinsic factor," vegetable protein was used.

Strauss⁴⁶ advocated transfusion of blood if there is an hunger or circulatory failure. To anemic patients 10 units of liver extract should be given intramuscularly for three days and then at weekly intervals until the blood count is normal. Larger doses are required to raise the red cell count to 5,000,000 per cubic millimeter. Frequently after twelve months of "normal" blood counts it is possible to increase the interval between injections to two weeks. Strauss advocated large doses of liver extract to arrest completely all progress of degeneration of the spinal cord. "It has been unequivocally established," he said, "that such arrest can be achieved if sufficient amounts of liver extract are employed." This would require 35 units intramuscularly during the first week and at least 10 units a week thereafter and double the dose if the neurologic lesions progress. This treatment must be continued for at least a year and reduced later with great caution. Iron should be added when a hypochromic condition develops. The U S P unit is the amount of material which when given daily will produce a satisfactory rise in the reticulocyte count and an adequate increase in the number of erythrocytes and the percentage of hemoglobin in selected patients with Addisonian pernicious anemia.

In the treatment of the neurologic manifestations, Schaller and Newman⁴⁷ injected 10 cc of liver extract intramuscularly once every three weeks, after the initial injections every three or four days for two or three weeks and then at weekly intervals during the first year. In none of their series of 40 patients studied over a period of five years was there any progression of the neural symptoms when adequate treat-

44 Klumpp, T. G. The Treatment of Pernicious Anemia with Autolyzed Liver Concentrate, *J A M A* **106** 1245 (April 11) 1936.

45 Henning, N., and Keilhack, H. Untersuchungen über eine rationelle Dauertherapie der perniziösen Anämie, *Arch f Verdauungskr* **59** 129, 1936.

46 Strauss, M. B. The Pharmacopeia and the Physician. The Use of Drugs in the Treatment of Anemia, *J A M A* **107** 1633 (Nov 14) 1936.

47 Schaller, W. F., and Newman, H. W. Liver Therapy for Combined Sclerosis, *Arch Int Med* **58** 45 (July) 1936.

ment was given. If neurologic symptoms do progress, it is a sign that treatment is inadequate.

Baserga⁴⁸ recommended injection of liver extract corresponding to 5,000 Gm a week or in a two week interval for patients with neurologic complications. In his opinion the daily intramuscular injections of liver extract corresponding to 700 Gm will prevent neurologic symptoms. The hemoglobin value for men should be kept at 100 per cent and that of women at 90 per cent. Large doses of iron and physical reeducation are advocated. It is suggested that discontinuance of therapy because of financial conditions is the main cause of the development of neurologic lesions.

Since there are spontaneous variations in the intensity of the neurologic manifestations without therapy, conclusions drawn from the benefits of specific treatment must be guarded. Improvement in the symptoms and objective arrest of the signs when adequate antianemia therapy is administered have been reported by Haden,⁴⁹ Mills⁵⁰ and Hyland and Farquharson.⁵¹ Adequate treatment means not only a normal red cell count and hemoglobin value but normal morphologic characteristics of the red blood cells. Russell⁵² noted sensory improvement after subcutaneous injections of large doses of vitamin B₁.

A summary of the effects of various types of therapy given to 577 patients with pernicious anemia was given by Sturgis and Isaacs.⁵³ In this group of patients there were 76 deaths during an eight year period. Thirty-seven, or 49 per cent, died of complications of pernicious anemia, especially lesions associated with changes in the central nervous system. Sturgis⁵⁴ stressed the importance of suiting the dose of liver extract to the individual patient.

48 Baserga, A. Contributo clinico allo studio delle sindromi nervose dell'anemia perniciosa, *Haematologica* **17** 603, 1936.

49 Haden, R. L. The Treatment of the Neuromuscular Sequelae of Pernicious Anemia, *S Clin North America* **16** 1077, 1936.

50 Mills, E. S. The Effect of Therapy on Nerve Degeneration in Pernicious Anemia, *Am J M Sc* **191** 72, 1936.

51 Hyland, H. H., and Farquharson, R. F. Subacute Combined Degeneration of Spinal Cord in Pernicious Anemia. Results of Treatment in Seventy-Four Consecutive Cases with Certain Clinical Observations, *Arch Neurol & Psychiat* **36** 1166 (Dec.) 1936.

52 Russell, W. R. The Parenteral Administration of Vitamin B₁ in the Treatment of Polyneuritis and Other Conditions, *Edinburgh M J* **43** 315, 1936.

53 Sturgis, C. C., and Isaacs, R. The Present Status of the Treatment of Pernicious Anemia Based on an Experience of Eight Years in Treating Five Hundred and Seventy-Seven Patients, *Tr Am Clin & Climatol A* **51** 28, 1935.

54 Sturgis, C. C. The Present Status of Pernicious Anemia. Experience with Six Hundred Cases over Eight Years, *Ann Int Med* **10** 283, 1936.

MACROCYTIC ANEMIA OTHER THAN PERNICIOUS ANEMIA

The various etiologic factors which may produce macrocytic anemia have been discussed in the current reviews of Davidson,⁵⁵ Muir⁵⁶ and Isaacs and his associates⁵⁷ Although Greenspon² suggested that an extrinsic factor was unnecessary, it is generally accepted that the substance required for the normal development of red blood cells is produced by the interaction of the extrinsic and intrinsic factors The product formed is absorbed from the intestine, stored in the liver and released to the body tissues for utilization as needed If there is a disturbance of any of the factors which are involved in this mechanism, macrocytic anemia will result

Although the nature of the extrinsic factor has not been identified, Napier⁵⁸ and Konstam and Gordon⁵⁹ demonstrated clinically that a commercially prepared autolyzed yeast product is a satisfactory source Any interference with the production of the intrinsic factor by the stomach may produce macrocytic anemia Bachman⁶⁰ reported a case of inflammation of the stomach and macrocytic anemia in an infant less than 1 year of age Tateno⁶¹ observed the changes in the blood following total gastrectomy in man and suggested the term agastric hypoplastic hyperchromic anemia Heck and Walters⁶² noted a satisfactory response to liver therapy in a woman in whom macrocytic anemia developed after gastric resection

The macrocytic anemias which have been observed clinically in association with disturbances of gastric function have been difficult to produce experimentally Bussabarger and Ivy⁶³ removed the stomachs of 8 monkeys, and microcytic anemia developed in all Hogs were gas-

55 Davidson, L S P Pernicious Anaemia and Other Macrocytic Anaemias, *Brit M J* **1** 804 (April 18) 1936

56 Muir, H E The Stomach and Anemias, *South M J* **29** 312, 1936

57 Isaacs, R, Sturgis, C C, Bethell, F H, and Goldhamer, S M Blood A Review of the Recent Literature, *Arch Int Med* **57** 1186 (June) 1936

58 Napier, L E Tropical Macrocytic Anaemia, *Lancet* **2** 679 (Sept 19) 1936

59 Konstam, G, and Gordon, H Idiopathic Steatorrhea with Skin Lesions and Megalocytic Anaemia, *Proc Roy Soc Med* **29** 629, 1936

60 Bachman, A L Macrocytic Hyperchromic Anemia in Early Infancy Report of Case and Review of Literature, *Am J Dis Child* **52** 633 (Sept) 1936

61 Tateno, S Ueber 3 Falle von Totalexstirpation des Magens, insbesondere uber deren postoperative Blutbefunde, *Arch f klin Chir* **184** 681, 1936

62 Heck, F J, and Walters, W Development of Macrocytic Anemia Following Resection of Stomach, *Proc Staff Meet, Mayo Clin* **11** 118 (Feb 19) 1936

63 Bussabarger, R A, and Ivy, A C Hematologic Studies on Gastrectomized Monkeys, *Proc Soc Exper Biol & Med* **34** 151, 1936

trectomized by Bence⁶⁴ During the first year postoperatively microcytic anemia developed, which gradually was replaced by macrocytic anemia The bone marrow of these animals was similar to that seen in patients with pernicious anemia during a relapse The stomachs of 45 rats were removed by Bussabarger and Jung,⁶⁵ and in all instances hypochromic anemia resulted This responded best to iron medication plus liver extract Several investigators gastrectomized dogs Petri and his co-workers⁶⁶ reported normochromatic anemia and also observed degenerative changes in the gray substance of the medulla Vlados and his colleagues⁶⁷ reported the development of both secondary and primary anemia after gastrectomy in dogs In their opinion the intrinsic factor is a ferment Fontes and his colleagues,⁶⁸ as well as Ducuing and his associates,⁶⁹ reported hypochromic anemia following the removal of the stomachs of dogs

The similarity of the blood picture in patients with pernicious anemia and in those with stricture of the intestine was observed by Faber in 1895 A series of 20 patients with various intestinal lesions associated with anemia has been reported on by Butt and Watkins⁷⁰ Eleven had primary anemia, and the remaining 9 had hypochromic anemia Hawksley and Meulengracht⁷¹ stated the opinion that the macrocytic anemia which is associated with intestinal strictures is due to impaired absorption or a progressive infection which causes gastritis, followed by atrophy of the gastric mucosa with failure of secretion of the intrinsic factor Konstam⁷² and Konstam and Gordon⁵⁹ noted megalocytic

64 Bence, G Die Beziehungen der experimentellen agastrischen Anämie zur Perniciosa, *Ztschr f klin Med* **130** 275, 1936

65 Bussabarger, R A, and Jung, F T Dietary and Hematologic Studies After Gastrectomy in the Rat, *Am J Physiol* **117** 59, 1936

66 Petri, S, Bøggild, D, and Ohlsen, A S Experimental Investigations on Gastrogenic Anemias (in Dogs) Results of Operative Removal Either of Whole Stomach Plus Brunner Gland Region in Duodenum, or of Fundus Region Only *Hospitalstid* **79** 509 (May 19) 1936

67 Vlados, H, Bagdasarov, A, Dulcin, M, and Bondarenko, E The Part Taken by the Stomach in the Regulation of Blood-Formation, *Acta med Scandinav* **88** 295, 1936

68 Fontes, G, Kunlin, J, and Thivolle, L Le métabolisme du fer et l'hématopoïèse chez le chien après gastrectomie totale et exclusive, *Sang* **10** 433, 1936

69 Ducuing, J, Miletzky, O, and Soula, C L'anémie agastrique expérimentale, *Sang* **10** 409, 1936

70 Butt, H R, and Watkins, C H Occurrence of Macrocytic Anemia in Association with Lesions of the Bowel, *Ann Int Med* **10** 222, 1936

71 Hawksley, J C, and Meulengracht, E Intestinal Stricture and Its Association with Pernicious Anaemia, *Lancet* **2** 124 (July 18) 1936

72 Konstam, G Idiopathic Steatorrhoea with Osteoporosis, Tetany and Megalocytic Anaemia, *Proc Roy Soc Med* **29** 631, 1936

anemia in patients with idiopathic steatorrhea Battaglia and Arata⁷³ observed progressive macrocytic anemia in a woman as a result of infestation with *Trichocephalus trichiuria*. After antiparasitic therapy the blood returned to normal, with no subsequent relapses noted for at least four years after treatment was discontinued.

The production of macrocytic anemia associated with experimental cirrhosis of the liver has been confirmed by Shumacker and Wintrobe.⁷⁴ These investigators also noted the presence of hyperplastic bone marrow, which is similar to the bone marrow associated with pernicious anemia during a relapse. There have also been several references⁷⁵ to an anemia in which there are a high color index and macrocytosis occurring in association with diseases of the liver. Box and Gill⁷⁶ cited a case of syphilitic hepatitis in which there was a response to antisiphilitic treatment only. Hatfield⁷⁷ reported a case of splenomegaly and anemia which were cured with oral and parenteral liver therapy. Israels and Wilkinson⁷⁸ described a syndrome characterized by macrocytic anemia, the presence of "free" hydrochloric acid in the gastric contents, hyperplastic bone marrow and failure to respond to the usual types of medication for this type of anemia. The disease has a chronic course with ultimate death. The authors substantiated their findings by citing 4 cases which fulfil the aforementioned requirements.

There appears to be sufficient evidence that the intrinsic factor may be present in the stomach, but owing to hepatic damage the hematopoietic substance cannot be stored and released to the body for utilization, and as a result macrocytic anemia develops. The treatment of the anemia associated with these various conditions depends on which factor or factors are contributing to the cause in each instance. If the intrinsic factor is absent, liver administered orally may be effective, however,

73 Battaglia, A, and Arata, E. C. Anemia perniciosa por tricocefalos trichiurus, *Prensa med argent* **23** 1094 (April 29) 1936.

74 Shumacker, H. B., Jr, and Wintrobe, M. M. Morphologic Changes in the Blood Associated with Experimentally Produced Hepatic Damage, *Bull Johns Hopkins Hosp* **58** 343, 1936.

75 Wintrobe, M. M. Relation of Disease of the Liver to Anemia. Type of Anemia, Response to Treatment, and Relation of Type of Anemia to Histopathologic Changes in Liver, Spleen and Bone Marrow, *Arch Int Med* **57** 289 (Feb.) 1936. Rosenberg, D. H. Macrocytic Anemia in Liver Disease, Particularly Cirrhosis. Observations on Incidence, Course and Reticulocytosis, with Correlated Study of Gastric Acidity, *Am J M Sc* **192** 86, 1936.

76 Box, C. R., and Gill, A. M. Severe Syphilitic Anaemia of the Pernicious Type, *Lancet* **1** 24 (Jan 4) 1936.

77 Hatfield, M. J. An Unusual Case of Secondary Anemia Simulating Primary Anemia, *Kentucky M J* **34** 76 1936.

78 Israels, M. C., and Wilkinson, J. F. Achrestic Anaemia, *Quart J Med* **5** 69, 1936.

if there is a disturbance of absorption or storage parenteral therapy should be instituted

The association of macrocytic anemia with nutritional defects incident to a variety of clinical conditions is reported by Bethell and Rottschaefer⁷⁹ Such conditions are generally characterized by a lowering of the albumin content of the serum, and the anemia may not result from a specific maturation defect They concluded that determination of serum proteins in conjunction with quantitative studies of the red blood cells often discloses the nature of macrocytic anemia and is of value in the selection of treatment

ANEMIA ASSOCIATED WITH OTHER DISEASE ENTITIES

HEMOLYTIC ANEMIA

The use of the term spherocytic icterus for the type of hemolytic jaundice marked by the presence of spheroid red blood cells and icterus has been suggested by Krumbhaar⁸⁰ The term is useful as well as descriptive

After splenectomy the hyperactivity of erythropoiesis in the bone marrow is decreased Totterman⁸¹ counted the relative number of developing red blood cells in the material obtained by sternal puncture and found 1,893 nucleated red blood cells for each 400 white blood cells before splenectomy, but seven months after the removal of the spleen the number fell to 110 Lowinger⁸² studied the marrow of 6 patients with the disease and found that the proportion of immature red blood cells was greatly increased In none of his studies did he observe any megaloblasts in the marrow of these patients

The intensive stimulus to blood regeneration in hemolytic jaundice may lead to extramedullary myelopoiesis Gleave⁸³ described the formation of large masses of bone marrow along dorsal vertebral bodies in a 28 year old man who died after the operative removal of a 43 ounce (1.3 Kg) spleen The masses, eight in all, lay behind the pleura and arose in the angle between the vertebral bodies and the ribs The blood

79 Bethell, F. H., and Rottschaefer, G. Interpretation of Macrocytosis with Especial Reference to Developmental Abnormalities of Red Blood Cell and to Hypoproteinemia Preliminary Report, Univ Hosp Bull, Ann Arbor **2** 65, 1936

80 Krumbhaar, E. B. Hemolytic Jaundice—Spherocytic Icterus, J. A. M. A. **107** 1739 (Nov 21) 1936

81 Totterman, G. Bone Marrow in Hemolytic Jaundice and Contribution to Question of Nature of Megaloblasts, Finska lak-sällsk handl **79** 686, 1936

82 Lowinger, S. Das Bild des Knochenmarkes bei der konstitutionellen hämolytischen Anämie (Ikterus Haemolyticus), Folia haemat **54** 27, 1935

83 Gleave, H. H. Paravertebral Heterotopia of Bone Marrow in a Case of Acholuric Jaundice, J Path & Bact **42** 538, 1936

supply was the same as that of the vertebral bodies, suggesting a direct extension of the marrow as a result of the intensive erythroblastic activity

Thompson⁸⁴ summarized the experience of the splenic disease clinic of the Presbyterian Hospital of New York with 45 patients. The symptoms of typical hemolytic jaundice were promptly, completely and permanently relieved by splenectomy, while those of the atypical forms were not. The hemolytic tendency in patients with spherocytosis may remain latent, first appearing at intervals from the age of 6 weeks to 58 years. When the disease was once active, spontaneous remission did not occur. The inverse relation was pointed out in man and animals between the mean diameter of the red blood cells and the strength of the solution of sodium chloride in which hemolysis begins.

ANEMIA ASSOCIATED WITH CANCER

The blood picture associated with cancer is not pathognomonic, nor does it give any information as to the site of the lesion or the extent of the malignant process. If anemia is present it may be either microcytic or macrocytic, and the color index may be low or high. There is usually leukocytosis. Mogensen⁸⁵ studied the blood of 75 patients with cancer of the stomach. Thirty-one per cent of the patients had no anemia. For the entire group the average hemoglobin value was 72.8 per cent. For those with anemia there appeared to be no relationship between the severity of the anemia and the age, sex or duration of the existence of the malignant growth. Thus the presence or absence of anemia was claimed to be of no clinical value in the diagnosis of a malignant process.

On the other hand, the type of anemia present may confuse the clinical picture considerably. Waugh⁸⁶ reported 2 cases of carcinoma of the bone marrow with resulting hemolytic anemia. Kiser and Rosenak⁸⁷ also noted a hemolytic type of anemia in cases of carcinoma of the stomach with metastasis to the bone marrow. The peripheral blood showed a diminution in the red cell count, with a corresponding decrease in the hemoglobin value. Many immature red and white blood cells were observed in studies of stained blood films. In these cases the fragility of the red blood cells was normal, although in similar instances

84 Thompson, W. P. Hemolytic Jaundice. Its Diagnosis, Behavior and Treatment, a Review of Forty-Five Cases, *J. A. M. A.* **107** 1776 (Nov. 28) 1936.

85 Mogensen, E. Anemia Associated with Cancer of Stomach, *Hospitalstid* **79** 85 (Jan. 28) 1936.

86 Waugh, T. R. Hemolytic Anemia in Carcinomatosis of the Bone Marrow, *Am. J. M. Sc.* **191** 160, 1936.

87 Kiser, E. F., and Rosenak, B. D. Myelophthisic Anemia in a Case of Carcinoma of the Stomach, *J. A. M. A.* **107** 963 (Sept. 19) 1936.

it has been reported as increased. Waugh suggested that the anemia is produced by a toxic substance. Kiser and Rosenak expressed the belief that it may be a compensatory phenomenon or an evidence of irritation of the bone marrow.

The differential diagnosis between pernicious anemia and carcinoma of the stomach is most difficult when the latter is associated with macrocytic anemia. Silverman⁸⁸ reported the case of a man who had been successfully treated for pernicious anemia for six years, and in whom carcinoma of the stomach then developed. This was substantiated by autopsy. A similar case was reported by van der Sande²². Silverman said he thought that the association of these two diseases may be coincidental, and he suggested that changes in the p_H alter the gastric wall and allow the development of carcinoma. There have been frequent references in the literature suggesting that the macrocytic anemia associated with carcinoma of the stomach is the result of interference in the production of the intrinsic factor in the stomach. Goldhamer⁸⁸ recently reported the absence of the intrinsic factor in the gastric contents of a patient who had macrocytic anemia associated with linitis plastica. The anemia was eliminated after the oral administration of desiccated stomach. Hulbert⁸⁹ reported a case of adenocarcinoma of the stomach associated with hyperchromic anemia in which there was no response either to liver or to iron.

Sugiura and Benedict⁹⁰ studied the effect of an anemia-producing diet on the growth of carcinoma, sarcoma and melanoma in animals. They concluded that the anemia per se did not affect the growth of tumors but that the rate of growth of the malignant process was dependent on the nutritive state of the animals. The rate of growth of tumors in animals on an inadequate diet and in a poor nutritive state was greatly retarded.

CHANGES IN THE BLOOD ASSOCIATED WITH INFECTION

The importance of cytoplasmic and nuclear changes which occur in the neutrophils in severe infectious states was emphasized by Mendell, Meranze and Meranze⁹¹. In their opinion the presence of toxic

88 Goldhamer, S. M. Linitis Plastica—the Absence of the Intrinsic Factor in the Gastric Contents, read at the meeting of the Michigan Academy of Letters, Science and Arts, March 1937.

89 Hulbert, N. G. Adenocarcinoma of the Stomach and Hyperchromic Anaemia, *Lancet* **2** 74 (July 11) 1936.

90 Sugiura, K., and Benedict, S. R. The Effect of an Anemia-Producing Diet on the Growth of Carcinoma, Sarcoma and Melanoma in Animals, *Am J Cancer* **26** 115, 1936.

91 Mendell, T. H., Meranze, D. R., and Meranze, T. Comparative Study of Cytoplasmic and Nuclear Changes in Neutrophils in Severe Infectious States, *Am J M Sc* **192** 316, 1936.

granules in the cytoplasm of the neutrophils, the vacuolation of the cytoplasm and the presence of bluish areas in the cytoplasm are a more reliable and accurate guide of the severity and prognosis of an infection than changes noted in the nuclei. The cytoplasmic changes appear to occur earlier in severe infections and last longer than the nuclear changes. As a substitute for the Schilling index the authors suggested the degenerative index—an equation with the number of degenerated neutrophils as the numerator and the total number of neutrophils as the denominator. The severity of the infection is thought to be mild, moderate, severe or grave if the number of neutrophils with cytoplasmic changes is 25, 50 or 75 per cent or more, respectively.

Gibson⁹² reported a case of acute hemolytic anemia, similar to Lederer's, in which the disease was due to dental sepsis. Studies of the blood were made by Goodrich and Smith⁹³ for patients with coronary occlusion. The average white blood cell count was from 13,000 to 18,000 per cubic millimeter. The highest leukocyte counts occurred in the fatal cases. Eosinophils were absent during the active process and present during convalescence. In the opinion of these authors the Schilling count may be used as an index for the prognosis.

In patients with peptic ulcer Ugelli⁹⁴ noted lymphocytosis and eosinophilia. He interpreted these findings not as being characteristic of ulcer but as an indication of the vagotonic constitution of the patient. The blood picture was altered by the complication of infection or hemorrhage which caused neutrophilia. These changes disappeared after operation. Totterman⁹⁵ observed the presence of immature myeloid cells and associated leukocytosis in cases of severe polyarthritis and pneumonia.

ANEMIA ASSOCIATED WITH ENDOCRINE DYSFUNCTION

The blood picture associated with thyroid dyscrasias has long been a subject of controversy. Many authors have observed a macrocytic anemia in conjunction with myxedema, while others have reported a microcytic anemia. The anemia may be directly related to the dysfunction of the thyroid gland, or it may exist as an independent condition. Holbøll⁹⁶ reviewed a series of 28 cases of myxedema. All the patients

92 Gibson, P. C. A Case of Acute Febrile Anaemia Due to Dental Sepsis, *Lancet* **1** 994 (May 2) 1936.

93 Goodrich, B. E., and Smith, F. J. Nonfilament Leukocyte Count After Coronary Artery Occlusion, *Am Heart J* **11** 581, 1936.

94 Ugelli, L. Distribuzione dei gruppi sanguigni negli individui portatori di ulcere gastroduodenali, *Policlinico (sez prat)* **43** 1591 (Sept 7) 1936.

95 Totterman, G. So-Called Myeloid Reaction, *Finska lak-sällsk handl* **79** 880, 1936.

96 Holbøll, S. A. Anemia in Myxedema Patients, *Acta med Scandinav* **89** 526, 1936.

were women. Their ages ranged from 35 to 64 years. The average duration of their symptoms was six years. Thirteen of the patients had hemoglobin levels below 70 per cent, and in 7 the range was between 70 and 79 per cent. The color index was normal or slightly less than normal in all instances. Eosinophilia was never observed. Lymphocytosis was usually present, the average number of lymphocytes being 50 per cent and the highest value observed 62 per cent. With the administration of thyroid the lymphocytes decreased in number. Holbøll noted also that the anemia associated with myxedema was most satisfactorily influenced by thyroid medication or by a combination of thyroid and iron. This observation was substantiated by the experiments of Bisgard and Sharpe⁹⁷. They thyroidectomized 32 rats, producing myxedema and associated macrocytic anemia. The anemia could not be eliminated with either liver extract or iron but readily responded to thyroid medication.

Zondek and Kaatz⁹⁸ noted an increase in the number of platelets in the circulating blood after the use of thyroid preparations. The increase occurred within from twenty-four to forty-eight hours and disappeared in seventy-two hours. The thyrotropic hormone of the pituitary gland was observed to have the same effect, but its action was more protracted. Epinephrine had a variable influence on the platelets. In some instances the number of platelets was increased, in others it was decreased.

HYPOCHROMIC AND MICROCYTIC ANEMIA OF THE IRON DEFICIENCY TYPE

Significant advances in the study of the defective formation of blood associated with a disturbed metabolism of iron have during the past year pursued three lines of inquiry: investigations concerning the absorption, storage and utilization of iron in experimental anemia, observations of the changes in the blood following gastric operations in man and in animals, and consideration of the factors involved in the lowering of blood values during pregnancy. The relationship of anemia to pregnancy will be discussed under a separate heading.

Whipple and Robschert-Robbins,⁹⁹ continuing their work on dogs subjected to prolonged repeated loss of blood, found that iron given

97 Bisgard, J. D., and Sharpe, J. C. Relation of Thyroid Gland to Hematopoiesis, *J. A. M. A.* **108**: 589 (Feb. 13) 1937.

98 Zondek, H., and Kaatz. Hormonal Regulation of Number of Blood Platelets in Blood, *Brit. M. J.* **2**: 387 (Aug. 22) 1936.

99 Whipple, G. H., and Robschert-Robbins, F. S. Iron and Its Utilization in Experimental Anemia, *Am. J. M. Sc.* **191**: 11, 1936.

intravenously to anemic and iron-depleted animals was returned quantitatively as newly formed hemoglobin on the basis of 10 mg of iron to 3 Gm of hemoglobin, regardless, within limits of tolerance, of the quantity of iron injected. When iron was given by mouth to these standard anemic dogs the effect on the production of hemoglobin was not proportional to the dose administered, the maximum utilization of iron being 35 per cent of an optimal dose of 40 mg daily for two weeks. They found that a whole liver supplement to inorganic iron given by mouth produced a summation effect which could not be accounted for solely by the iron content of the liver. However, of especial interest is their observation that no such summation effect followed the feeding of liver concurrently with the intravenous administration of iron. Apparently the stimulus to erythropoiesis occasioned by the presence of relatively large amounts of iron in the circulating blood was maximal and therefore could not be augmented by the usually omnipotent liver. The importance of this conclusion lies in its intimation that liver in the treatment of the anemia of chronic hemorrhage supplies no deficiency but that its effectiveness in supplementing iron depends on promotion of the absorption or utilization of the metal.

Whipple and Robschey-Robbins found no difference in the effectiveness of iron given by mouth whether in the ferrous, ferric or reduced state. The formation of an Eck fistula or removal of the spleen reduced the utilization of iron given by vein.

Although the work of these investigators on standard anemic dogs advances materially the understanding of the metabolism of iron, the direct application of their findings to clinical practice is hazardous. As they pointed out, the apparently superior results gained from the intravenous over the oral administration of iron in their experiments does not justify the adoption of this route in the treatment of patients. Iron by vein is decidedly toxic, and, moreover, one is not greatly concerned with a maximal percentage of utilization of therapeutic preparations of iron. A daily conversion of 25 or 30 mg of iron into hemoglobin is optimal, although one may give from five to fifty times this amount.

The uniform effectiveness of iron, regardless of its chemical state, is presumably dependent on reduction to the ferrous form by a normally functioning stomach possessed by dogs made anemic by bleeding but not by those patients who present the more difficult therapeutic problems. Furth and Scholl¹⁰⁰ determined the absorption of ferrous and ferric compounds from ligated loops of rabbits' intestines. The range of percentage of absorption of the ferrous preparations was from 76 to

100 Furth, O, and Scholl, R. Absorption of Ferrous and Ferric Compounds from the Intestines of Rabbits, *J Pharmacol & Exper Therap* **58** 14, 1936

39.7, the absorption of ferric compounds, from 30.5 to 19.8. Absorption of ferrous iron was decidedly impaired by an acid reaction of the intestinal contents.

Iron in the animal economy appears to play three distinct physiologic rôles. That contained in hemoglobin normally constitutes the greatest portion and is concerned with the transference of oxygen, that possessed by the parenchyma cells and by hemoglobin in the muscle is required for local cell metabolism, and that stored in the liver, spleen and elsewhere forms an inactive reserve to be used primarily in the replacement of hemoglobin in the blood stream. Hahn and Whipple¹⁰¹ found in the case of their standard anemic dogs that there was a rapid turnover of iron in the tissues. After iron supplements were fed for short periods, no storage of the metal was found in the liver, the absorbed iron was formed almost immediately into hemoglobin. Even after longer experiments only small amounts of iron were stored so long as there was a need for hemoglobin. Iron given by vein was stored to a large extent in the liver and spleen. The iron contained within parenchyma cells and hemoglobin of the muscles is not drawn on, no matter how severe the anemia. Moreover, the intravenous administration of iron results in no surplus storage in this tissue.

Schultze, Elvehjem and Hart¹⁰² found that rats made severely anemic by a diet deficient in iron and copper had depleted stores of copper. The feeding of iron and copper for seven days caused only a 5 per cent retention of copper, although maximum hemoglobin formation occurred. Similar experiments on pigs revealed that a deficiency of iron but not of copper could be corrected with iron alone. When both iron and copper were deficient, both were required for cure of the anemia, but there was no apparent storage of the copper in the bone marrow. In a subsequent paper the same authors¹⁰³ reported that the copper content of the blood of pigs suffering from nutritional anemia due to iron and copper deficiency falls to extremely low levels. Apparently a minimum copper level of the blood is required for rapid continued erythropoiesis to take place.

Investigation of the changes in the blood produced experimentally by operations on the digestive tract have been carried out by Kellogg,

101 Hahn, P. F., and Whipple, G. H. Iron Metabolism. Its Absorption, Storage and Utilization in Experimental Anemia, *Am J M Sc* **191** 24, 1936.

102 Schultze, M. O., Elvehjem, C. A., and Hart, E. B. Studies on the Copper and Iron Content of Tissues and Organs in Nutritional Anemia, *J Biol Chem* **116** 93, 1936.

103 Schultze, M. O., Elvehjem, C. A., and Hart, E. B. Studies on the Copper Content of the Blood in Nutritional Anemia, *J Biol Chem* **116** 107, 1936.

Mettier and Purviance¹⁰⁴ Working with dogs, they combined the experimental methods of Whipple, based on repeated bleeding and standard diets, with gastrectomy They found that after removal of the stomach the capacity to produce hemoglobin on a beef-supplemented diet was greatly reduced Alt¹⁰⁵ found that resection of 40 per cent of the small intestine of rats produced no anemia When, however, 80 per cent was removed, anemia, usually hypochromic, developed, which he attributed chiefly to impaired absorption of iron A further report on the effects of gastrectomy in the rat has been made by Bussabarger and Jung⁶⁵ After removal of the stomach, nutrition was seriously impaired, and severe microcytic hypochromic anemia developed Iron by mouth or by injection had a beneficial effect on the anemia, whereas liver extract and vitamins, among other substances, were of no value

One hundred and twenty patients with achylic chloranemia and 200 patients with pernicious anemia were considered by Fleischhacker and Klima¹⁰⁶ with reference to a previous history of gastro-intestinal operations In 18 of those with achylic chloranemia, anemia developed after operation, all were women Nine patients, 4 of them men, acquired pernicious anemia after operation These authors stated the opinion that a mere diminution in the size of the stomach by surgical removal is not a sufficient cause for anemia One of their patients had polycythemia after almost total resection of the stomach Frequently secondary changes occur at the site of the operation, and in their opinion these are the principal causes of the anemia

Approaching the problem from the converse aspect, Lublin¹⁰⁷ studied the blood of 46 patients who returned to the clinic for various complaints other than hemorrhage after either gastro-enterostomy, with or without exclusion of the pylorus, or a Billroth II operation Sixty-nine per cent of these patients had hypochromic anemia Lowered blood values were especially prevalent among those who had had a Billroth II operation or an operation for exclusion of the pylorus Females were predominantly affected Although achlorhydria or hypochlorhydria was usually present in these cases of anemia, 4 patients secreted a normal amount of hydrochloric acid Postoperative intestinal disturbances bore no relation to the occurrence of anemia Lublin claimed that the causes

104 Kellogg, F, Mettier, S R, and Purviance, K Studies on Hypochromic Anemia in Dogs Evaluation of Standard Bread Diet and of Meat Diet on Formation of Hemoglobin Before and After Gastrectomy, *J Clin Investigation* **15** 241, 1936

105 Alt, H L Extensive Resection of Small Intestine in Rat with Special Reference to Anemia, *Am J Digest Dis & Nutrition* **3** 169, 1936

106 Fleischhacker, H, and Klima, R Ueber Anamien nach Magen- und Darmoperationen, *Ztschr f klin Med* **129** 227, 1935

107 Lublin, H On Anemia Following Gastric Operations, *Am J Digest Dis & Nutrition* **3** 8, 1936

of this type of anemia are to be found chiefly in the stomach, duodenum, liver and perhaps pancreas

Additional evidence of the rôle of the normally functioning stomach in the absorption of iron is afforded by the work of Kellogg and Mettler¹⁰⁸ They found that food iron was not utilized for hemoglobin regeneration by patients treated for peptic ulcer with an alkaline regimen The hemoglobin value increased after discontinuance of the alkali Their observations are of more theoretical than practical importance, since medicinal iron in suitable doses is effectively utilized in spite of alkali therapy Schjødt¹⁰⁹ reported the results of treatment in Meulengracht's clinic for patients with peptic ulcer complicated by hemorrhage Those treated even from the first day of hemorrhage with a general diet consisting of strained food, and ferrous lactate, 0.5 Gm three times a day, showed a gain in the blood count, especially the color index, and in general well being much more rapidly than those who received a progressive Sippy type of treatment with the same quantity of medicinal iron He did not mention the use of alkali

Ahlbom¹¹⁰ questioned 150 women with squamous cell carcinoma of the mouth, pharynx or esophagus concerning previous signs of simple achlorhydric anemia and the Plummer-Vinson syndrome Seventy per cent gave affirmative replies He suggested that these conditions may be precancerous Rasmussen¹¹¹ found a 12 per cent incidence of hypochromic anemia among 460 patients with pulmonary tuberculosis, 60 per cent of these were cured of anemia by iron therapy There was no evidence that the tuberculous process in itself had a deleterious effect on erythropoiesis In some instances there appeared to be a relationship between anemia and intestinal tuberculosis

No recent advances of importance have been made in the treatment of anemia due to iron deficiency The subject has been considered by Witts,¹¹² Strauss,⁴⁶ Bloedorn¹¹³ and Lucas and Henderson¹¹⁴ In

108 Kellogg, F, and Mettler, S R Effect of Alkaline Therapy for Peptic Ulcer on Utilization of Dietary Iron in Regeneration of Hemoglobin, *Arch Int Med* **58** 278 (Aug) 1936

109 Schjødt, E Blood Regeneration in Patients with Hematemesis or Melena from Peptic Ulcer, Treated with Usual Ulcer Cure and with Meulengracht Treatment, *Am J M Sc* **192** 163, 1936

110 Ahlbom, H E Simple Achlorhydric Anaemia, Plummer-Vinson Syndrome, and Carcinoma of the Mouth, Pharynx, and Oesophagus in Women Observations at Radiumhemmet, Stockholm, *Brit M J* **2** 331 (Aug 15) 1936

111 Rasmussen, H Anemia in Patients with Pulmonary Tuberculosis, *Norsk mag f lægevidensk* **97** 1125, 1936

112 Witts, L J Therapeutic Action of Iron, *Lancet* **1** 1 (Jan 4) 1936

113 Bloedorn, W A Rôle of Iron in Treatment of Anemia, *Minnesota Med* **19** 5, 1936

114 Lucas, G H W, and Henderson, V E On Administration of Iron, *Canad M A J* **34** 53, 1936

general, there has been a trend toward the use of the more stable ferrous preparations given in divided doses to supply approximately 160 mg of metallic iron daily. Patek¹¹⁵ has presented clinical evidence of the beneficial effect of chlorophyll and its derivatives as supplements to inorganic iron. In his opinion these pigments, preformed, can be used by the body in the production of erythrocytes.

Nutritional anemia in infancy is generally regarded primarily as an iron deficiency state. The clinical studies of Paxton¹¹⁶ and of Guest and Brown¹¹⁷ have added further support to this view and have increased the weight of evidence against the therapeutic value of copper. Continuing their work on the iron and copper content of human blood, Sachs, Levine and Fabian¹¹⁸ found in the blood of 6 new-born infants an average iron content of 51.79 mg per hundred cubic centimeters and an average hemoglobin value of 15.45 Gm per hundred cubic centimeters. Seventy-one children, varying in age from 1½ months to 15 years, showed an average of 40.51 mg of iron and 12.09 Gm of hemoglobin per hundred cubic centimeters. As in the case of adults, the authors found that copper and iron maintain a reciprocal relationship in the blood of normal children.

Orten, Smith and Mendel¹¹⁹ found polycythemia and concurrent hemoglobin deficiency in young rats fed a mineral-deficient ration. The changes, they claimed, were due chiefly, if not entirely, to a lack of calcium and iron. They suggested that calcium may favorably affect the economy of iron in metabolism.

A comprehensive review of the subject of anemia in infancy and early childhood has been published by Josephs¹²⁰.

ANEMIA OF PREGNANCY

In the study of anemia associated with pregnancy, increasing recognition has been given to the multiplicity of factors involved in the

115 Patek, A. J., Jr. Chlorophyll and Regeneration of the Blood. Effect of Administration of Chlorophyll Derivatives to Patients with Chronic Hypochromic Anemia, *Arch Int Med* **57** 73 (Jan) 1936.

116 Paxton, W. T. W. Nutritional Anaemia in Infancy and Childhood, *Glasgow M. J.* **125** 153, 1936.

117 Guest, G. M., and Brown, E. W. Erythrocytes and Hemoglobin of the Blood in Infancy and in Childhood. Size and Hemoglobin Content of Erythrocytes in Nutritional Anemia, *Am J Dis Child* **52** 616 (Sept) 1936.

118 Sachs, A., Levine, V. E., and Fabian, A. A. Copper and Iron in Human Blood. Normal Children, *Arch Int Med* **58** 523 (Sept) 1936.

119 Orten, J. M., Smith, A. H., and Mendel, L. B. Relation of Calcium and of Iron to Erythrocyte and Hemoglobin Content of Blood of Rats Consuming Mineral Deficient Ration, *J Nutrition* **12** 373, 1936.

120 Josephs, H. W. Anemia of Infancy and Early Childhood, *Medicine* **15** 307, 1936.

lowering of the blood values during gestation Feldman, van Donk Steenbock and Schneiders¹²¹ determined the hemoglobin value, cell volume and refractive index of the blood of 20 pregnant women and found evidence of hydremia regularly The maximum changes occurred at about the two hundred and twentieth day of gestation On the other hand, there were few or no signs of blood dilution among 40 pregnant cows

Boycott¹²² found that of 222 pregnant women attending the University College Hospital, London, 22 per cent had hemoglobin values below 11 Gm per hundred cubic centimeters He agreed with earlier investigators that the increased volume of plasma may produce an apparent anemia and that the effects of hydremia may coexist with true hypochromic anemia The common anemia of pregnancy, he found, responded well to adequate iron therapy In New Zealand a 14 per cent incidence during pregnancy of hemoglobin values below 10.28 Gm per hundred cubic centimeters was reported by McGeorge¹²³ He considered that lowered gastric acidity is the principal factor in the etiology of hypochromic anemia of pregnant women, dietary iron is important and contributory causes are diets low in protein and green vegetables and the added demand for iron occasioned by the gravid state Corrigan and Strauss¹²⁴ studied 200 women during the last four months of pregnancy Alternate patients were given 0.5 Gm of ferrous sulfate daily The others received placebos Of the 100 women taking iron, none had a hemoglobin value of less than 10.9 Gm per hundred cubic centimeters after delivery, of those not receiving iron, 24 had post partum a value of less than 10.9 Gm They concluded that hypochromic anemia in pregnancy may be largely prevented by the routine administration of iron, especially in the later months of gestation

Adair, Dieckmann and Grant¹²⁵ calculated the effect of hydremia and gave average and minimum normal blood values which may be expected during pregnancy Their incidence of anemia was 11.6 per cent, predominantly of the hypochromic and microcytic type Iron therapy was not always effective, and transfusions were frequently found of value They suggested that a dietary deficiency other than a lack

121 Feldman, H., van Donk, E. C., Steenbock, H., and Schneiders, E. F. Hydremia as Factor in Anemia of Pregnancy, *Am J Physiol* **115** 69, 1936

122 Boycott, J. A. Anaemia in Pregnancy, *Lancet* **1** 1165 (May 23) 1936

123 McGeorge, M. Anaemia in Gynaecological and Obstetric Practice in New Zealand, *J Obst & Gynaec Brit Emp* **42** 1027, 1935

124 Corrigan, J. C., and Strauss, M. B. Prevention of Hypochromic Anemia in Pregnancy, *J A M A* **106** 1088 (March 28) 1936

125 Adair, F. L., Dieckmann, W. J., and Grant, K. Anemia in Pregnancy, *Am J Obst & Gynec* **32** 560, 1936

of iron may be operative in these cases. Stevenson¹²⁶ analyzed 90 cases of anemia of pregnancy and described 60 as cases of hypochromic anemia and 30 as cases of "pernicious anemia of pregnancy." The latter differed from cases of typical pernicious anemia, and she attributed them to dietary defects. It should be noted that the high incidence of this form of anemia indicates that it was not the type commonly designated as pernicious anemia of pregnancy.

Studies of the blood of 66 pregnant women have been reported by Bethell¹²⁷. Although apparently healthy, 70 per cent of the subjects had blood values too low to be accounted for reasonably by the increased volume of plasma alone. Twenty-eight patients had hypochromic and microcytic anemia. By calculating the amount of iron required by the fetus and subtracting that saved by the absence of menstruation, it was shown that the net loss of iron suffered by the pregnant woman was no greater than that occasioned by serving as donor for a moderate-sized blood transfusion. Data were presented which demonstrated no correlation between the capacity of the stomach to secrete hydrochloric acid and the level of the blood count, thus suggesting that the temporary reduction of the gastric acidity was not a direct cause of lowered blood values in pregnancy. The development of hypochromic anemia during pregnancy was attributed to preexisting iron depletion, and it was suggested that a lack of iron may be recognized before the development of actual anemia by the presence of a lowered color index or of red blood cells of less than normal size. In such cases the administration of iron was recommended. A contrasting type of anemia occurred in 18 of the subjects, characterized by a normal color index and by erythrocytes of normal or increased size. The albumin content of the serum of these patients was abnormally low, and it was suggested that the anemia was caused by an inadequate intake of protein of high biologic value. Supplementing the dietary protein led to correction of the anemia.

Further emphasis of the relative unimportance of pregnancy as a cause of iron deficiency, except in cases of gross postpartum hemorrhage, has been provided by the work of Fullerton¹²⁸. He found hypochromic anemia prevalent among a group of 1,534 women of the poorer classes of Aberdeen, Scotland. The incidence and severity of the anemia increased with the age of the subjects until the menopause but bore no relation to the number of pregnancies. He attributed the anemia to

126 Stevenson, M. Investigation of Anaemias of Pregnancy and Puerperium, *J. State Med.* **44**:467, 1936.

127 Bethell, F. H. Blood Changes in Normal Pregnancy and Their Relation to Iron and Protein Supplied by Diet, *J. A. M. A.* **107**:564 (Aug. 22) 1936.

128 Fullerton, H. W. Anaemia in Poor Class Women, with Special Reference to Pregnancy and Menstruation, *Brit. M. J.* **2**:523 (Sept. 12) 1936, Hypochromic Anaemias of Pregnancy and Puerperium, *ibid.* **2**:577 (Sept. 19) 1936.

a diet low in iron, averaging for this group a daily intake of 7.71 mg of the metal, and to the loss of iron throughout reproductive life. He concluded

Menstruation constitutes an iron loss at least as great as that due to pregnancy and lactation even in women of the poorer classes the transference of iron from the mother to the uterus and its contents is compensated wholly or to a large extent by dietary iron. In cases where this demand exceeds the retention of dietary iron the degree of maternal iron deficiency which results is only slight. Where hypochromic anemia in pregnancy is marked, anemia has probably existed before the pregnancy, but has been made more apparent by physiological hydremia.

The incidence of symptoms of toxemia of pregnancy was related to the presence of hypochromic anemia in a series of cases reported by Moore and Williams.¹²⁹ Only 1 of 35 patients treated with iron showed symptoms of toxemia, whereas symptoms of a mild to a moderate degree of toxemia were noted in 6 of 34 untreated patients. However, it has been the experience of most observers that no obvious relationship exists between the common forms of anemia in pregnancy and the occurrence of toxemia. It seems more probable that the rarer grave anemias of pregnancy may have their origin in toxemia.

Daniachi¹³⁰ reported 6 cases of severe anemia not characterized by hypochromia. The bone marrow in these cases revealed either megaloblastic or normoblastic hyperplasia. The author claimed that aside from pernicious anemia of pregnancy, these anemias are of widely different types. They are all closely associated with toxemia, and their outcome depends on the result of the underlying toxic condition. Adequate prepartal care, he maintained, is the best prophylaxis of these severe anemias.

Heilbrun¹³¹ reported a case of pernicious anemia of pregnancy in which studies of the bone marrow revealed megaloblastic hyperplasia. After remission had been induced by the parenteral administration of liver extract, the marrow picture returned to normal.

DEFINITE DISEASE ENTITIES OF THE BLOOD

POLYCYTHEMIA

A patient who showed well marked symptoms of polycythemia for fifteen years is reported on by Welbourn.¹³² There were no marked

129 Moore, J, and Williams, E. M. P. Anaemia and Toxaemia of Pregnancy, *Brit M J* **2** 528 (Sept 12) 1936

130 Daniachi, M. A. Blutbildung und klinischer Verlauf der Graviditätsanämien, *Monatschr f Geburtsh u Gynak* **100** 328, 1935

131 Heilbrun, N. State of Sternal Bone Marrow in Case of Macrocytic (Pernicious) Anemia of Pregnancy, *J A M A* **107** 27 (July 4) 1936

132 Welbourn, M. A. Polycythemia Vera. Report of an Unusual Case, in *Medical Papers Dedicated to H. A. Christian, Physician and Teacher, in Honor of His Sixtieth Birthday*, Baltimore, Waverly Press, Inc, 1936, p 632

remissions, either spontaneous or induced, and no significant changes in the vascular system were noted

Dustin¹³³ has added another case of polycythemia in which anemia developed to those previously described by others. The red blood cell count was 6,840,000 per cubic millimeter originally. No splenic enlargement was noted. During the course of two years a red blood cell count of 2,300,000 per cubic millimeter was reached, with a color index of 0.56. Improvement followed the use of iron therapy. (Intestinal hemorrhage was probably an important etiologic factor.) In a 20 year old woman with pulmonary arteriolar sclerosis, dilatation of the pulmonary artery and hypertrophy of the right ventricle, Darley and Doan¹³⁴ found a red blood cell count of 7,480,000 per cubic millimeter. A curious feature was the abnormally high intake of salt (as much as 3 pounds [1.3 Kg.] in one week) to which the patient was accustomed.

Additional cases of polycythemia and duodenal ulcer are described by Kraemer and Asher¹³⁵. Biweekly gastric lavage with solution of sodium bicarbonate for three months did not influence the height of the red blood cell count (8,750,000 to 9,500,000 per cubic millimeter).

Herzog¹³⁶ fed his polycythemic patients on diets containing only 0.7 Gm of animal protein per day. He obtained improvement in the symptoms within one week and reduction in the number of red blood cells to normal in from two to nine weeks. The cases included both the Geisbock and the Vaquez type of polycythemia. After one or two months the intake of milk, fish and cheese was increased without harm.

Two women with an expanding intracranial lesion and polycythemia were reported on by Barker and Craig¹³⁷. The volume of blood was normal, and splenomegaly was absent. The red blood cell counts were 9,160,000 and 6,560,000 per cubic millimeter, respectively.

Emile Weil¹³⁸ studied a patient aged 56 years with a red blood cell count of 8,070,000 per cubic millimeter and with an enlarged spleen.

133 Dustin, P, Jr. A propos d'un cas d'anémie apparue chez un ancien hyperglobulique, *Sang* **10** 517, 1936.

134 Darley, W, and Doan, C. A. Primary Pulmonary Arteriosclerosis with Polycythemia, Associated with the Chronic Ingestion of Abnormally Large Quantities of Sodium Chloride (Halophagia), *Am J M Sc* **191**:633, 1936.

135 Kraemer, M, and Asher, M. Association of Erythremia and Duodenal Ulcer, *Am J M Sc* **191** 234, 1936.

136 Herzog, F. Die Behandlung der Polyzythämie mit an tierischem Eiweiss sehr armer Diät, *Deutsche med Wchnschr* **62** 960 (June 12) 1936.

137 Barker, N. W, and Craig, W. M. Relative Polycythemia Associated with Hypophyseal and Diencephalic Lesions, *Proc Staff Meet, Mayo Clin* **11** 548 (Aug 26) 1936.

138 Weil, P. E. Un cas de splénomégalie avec polyglobulie terminée en syndrome d'anémie type von Jaksch-Luzet, *Sang* **10** 752, 1936.

Large doses of x-rays over the spleen did not reduce the red blood cell count. No improvement followed liver or spleen therapy. The red blood cell count was reduced to normal with phenylhydrazine, and later the spleen was removed. Polycythemia returned. Roentgen therapy was given over the bones. Severe anemia with a leukemic blood picture followed (nucleated cells, 103 400 per cubic millimeter). The history in this case illustrates the interrelationships of polycythemia, leukemia and forms of anemia.

Liver extract, and to a less extent desiccated hog stomach, produced a temporary fall in the number of red blood cells in rats which had been made polycythemic by the administration of a milk diet supplemented by salts of cobalt, iron, copper and manganese (Marshall¹³⁹). The decrease (13 per cent) was maintained only until the administration of liver extract was stopped, after which the polycythemia returned. Fresh whole liver caused a temporary increase in the erythrocyte count, but fresh lean meat produced no change. Marshall concluded that the liver produces a hormone which exercises an inhibiting action on hematopoiesis.

That the gastric juice in polycythemia is rich in the "intrinsic factor of Castle" was concluded by Barath and Fulop,¹⁴⁰ after inducing remissions in pernicious anemia by the rectal administration of a beef digest from the stomachs of polycythemic patients. The loss of gastric juice had a favorable but temporary effect on the polycythemic patients.

In fish, frogs, dogs and men asphyxia is followed by a slight increase in the red blood cell count (Binet and Strumza¹⁴¹).

In 9 cases of polycythaemia vera Bowie¹⁴² found an average value for serum calcium of 11.3 mg per hundred cubic centimeters. The values were reduced after treatment with phenylhydrazine hydrochloride. The total values for plasma proteins were within normal limits (average, 6.68 Gm per hundred cubic centimeters). The average specific gravity of the serum was 1.025, but that of the whole blood was elevated to an average of 1.068.

The erythrocyte and leukocyte counts for rats made polycythemic with cobalt are decreased by roentgen therapy, just as in the case of

139 Marshall, L. H. Antianemic Treatment in Experimental Polycythemia, *Am J Physiol* **114** 194, 1935.

140 Barath, E., and Fulop, J. Untersuchungen über den pathogenetischen Zusammenhang von perniziöser Anämie und splenomegaler Polycythämie, *Ztschr f klin Med* **129** 172, 1935.

141 Binet, L., and Strumza, M. V. La polyglobulie asphyxique, son degré sa généralité, *Sang* **9** 927, 1935.

142 Bowie, M. A. Polycythemia Vera. A Study of the Relationship Between Serum Calcium and Total Proteins of the Serum, in *Medical Papers Dedicated to H. A. Christian, Physician and Teacher, in Honor of His Sixtieth Birthday*, Baltimore, Waverly Press, Inc., 1936, p. 626.

normal rats De Savitsch and his co-workers¹⁴³ found that cobalt did not enhance the regeneration of hematopoietic bone marrow after irradiation but that shielded parts of the bones after irradiation showed compensatory hyperplasia greater than that in the controls

Irradiation of the body as a whole—"spray therapy"—was used by Hunter¹⁴⁴ in 2 cases of polycythaemia vera and 1 case of Cooley's erythroblastic anemia About 1,000 roentgens was given over several weeks Remissions lasting three years were noted

PURPURA HAEMORRHAGICA

The etiology of purpura is manifold, and as a result various types have been described The clinical value of the innumerable complex classifications is doubtful There are three factors which determine the degree of bleeding (*a*) the platelets, (*b*) the permeability of the capillaries and (*c*) the plasma The reduction of the number of platelets is ascribed to a dysfunction of the bone marrow with decreased formation of platelets or to an increased destruction by the reticulo-endothelial system (primarily the spleen)

Purpura may be congenital or acquired Sanford, Leslie and Crane¹⁴⁵ described the case of an infant born with purpura Both the mother and the grandmother had a similar condition Three patients with purpura produced by *Bacillus pertussis* vaccine were observed by Kugelmass¹⁴⁶ Toxic purpura complicating scarlet fever was noted by Morrish¹⁴⁷ In some instances purpura may be produced by drugs Falconer, Epstein and Wever¹⁴⁸ described two types of purpura following the use of arsenicals In some instances the number of platelets is reduced, while in others there is damage to the capillaries Thrombopenia following the use of sedormid (allylisopropylacetylcarbamide)

143 de Savitsch, E , Radford, M , Blocksom, B H , Perry, S P , and Tupikova, N The Effect of Roentgen Irradiation on Experimentally Produced Polycythemia in Rats with Special Reference to Blood and Bone Marrow, *Am J Roentgenol* **35** 786, 1936

144 Hunter, F T "Spray X-Ray Therapy" in Polycythemia Vera and in Erythroblastic Anemia, *New England J Med* **214** 1123 (June 4) 1936

145 Sanford, H N , Leshe, E I, and Crane, M M Congenital Thrombocytopenia, *Am J Dis Child* **51** 1114 (May) 1936

146 Kugelmass, I N Thrombocytopenic Purpura Induced by Pertussis Toxin in Allergic Children, *J A M A* **107** 2120 (Dec 26) 1936

147 Morrish, J E Toxic Purpura Haemorrhagica Complicating Scarlet Fever, *Lancet* **1** 949 (April 25) 1936

148 Falconer, E H , Epstein, N N , and Wever, G K Purpura Haemorrhagica Following the Administration of Neoarsphenamine The Reaction to Neoarsphenamine Compared with the Reaction to Mapharsen, *Arch Int Med* **58** 495 (Sept) 1936

and phenobarbital has been described by Boas and Elf¹⁴⁹ Often the etiology of purpura is not known Finochietto and his colleagues¹⁵⁰ reported the association of exophthalmic goiter and purpura They were unable to explain the etiology of purpura, although in their opinion the thyroid dysfunction was not the causative factor Guggisberg¹⁵¹ described abnormal generalized bleeding complicated by pregnancy In his opinion pregnancy may improve or exacerbate the existing purpuric condition

The symptoms associated with purpura are varied, depending on the location and severity of the hemorrhages, the etiology of the condition and any existing diseases which may be present A case of intussusception following intra-abdominal hemorrhage was observed by Gray¹⁵²

In an effort to determine the etiology of thrombocytopenic purpura, Tocantins¹⁵³ experimentally produced the condition in dogs and observed the cytologic and physical changes in the blood The animals were given injections of a prepared antiplatelet serum by various routes—intravenous, intraperitoneal and subcutaneous With the first method the changes occurred most rapidly Thrombopenia developed within a few minutes and lasted for from forty-eight to seventy-two hours In from three to five days the number of platelets returned to normal, and it then exceeded the normal level for approximately fourteen days A peak was noted between the eighth and the twelfth day Macroplatelets appeared in three or four hours They varied greatly in shape, size and consistency Hemolysis occurred during the acute stage At first leukopenia existed, with a reduction in the number of lymphocytes, monocytes and eosinophils This was followed by leukocytosis in which the polymorphonuclear cells were greatly increased in number The bleeding time was markedly prolonged Tocantins concluded that there was a high correlation between the number of platelets and the degree of clot retraction and also a similar relationship between the clot retraction and the mean bleeding time In his opinion the permeability of the vessels, capillary and venous pressure, osmotic pressure, viscosity of the

149 Boas, E. P., and Elf, L. A. Thrombocytopenic Purpura Following Medication with Sedormid and with Phenobarbital, *New York State J. Med.* **36** 491 (April 1) 1936

150 Finochietto, R., del Castillo, E. B., and Parodi, A. S. Bocio exoftálmico y purpura hemorrágica trombocitopenica, *Semana med.* **2** 1059 (Oct 15) 1936

151 Guggisberg, H. Die gynakologische und geburtshilfliche Bedeutung der essentiellen thrombopenischen Purpura, *Helvet. med. acta* **3** 375, 1936

152 Gray, T. Henoch's Purpura Causing Acute Obstruction Twice in Eight Days, *Lancet* **1** 841 (April 11) 1936

153 Tocantins, L. M. Experimental Thrombopenic Purpura in the Dog, *Arch. Path.* **21** 69 (Jan.) 1936, Experimental Thrombopenic Purpura Cytological and Physical Changes in the Blood, *Ann. Int. Med.* **9** 838, 1936

blood and tension of the tissues were important factors in the determination of the bleeding

Since the etiology of purpura cannot always be determined, treatment frequently results in failure. Many investigators¹⁵⁴ have reported spectacular improvement after splenectomy. Hedenius and Wilander¹⁵⁵ suggested the use of small repeated amounts of heparin to prevent the postoperative formation of thrombi. Klima¹⁵⁶ observed satisfactory results with kephrine hydrochloride when administered orally or intramuscularly. Riolo¹⁵⁷ recommended increasing daily intravenous doses of epinephrine. He stated that the drug regulates the functions of the spleen—more platelets are expelled, the lytic action is decreased, the tone of the capillaries is increased and the bone marrow is stimulated to produce more thrombocytes. Phenylhydrazine was employed by Wallgren¹⁵⁸. Although the platelets were increased in number with this drug, there was an accompanying hemolysis. He concluded, therefore, that this type of therapy should not be employed. Clerc and his associates¹⁵⁹ injected intravenously pure octylic alcohol in small amounts into 10 patients with purpura. Although the coagulation time was shortened, there was little if any effect on the bleeding time. The mode of action was obscure. Lowenbuig and Ginsburg¹⁶⁰ noted the return to normal of all blood values after induced hypercalcemia. They advised the use of calcium gluconate to prevent the development of the toxic symptoms which are produced by parathyroid extract.

154 Brown, D. N., and Elliott, R. H. E. The Results of Splenectomy in Thrombocytopenic Purpura. Comparative Study of Ten Cases in Which Splenectomy Was Performed and Eleven Cases Treated by Conservative Methods, *J. A. M. A.* **107** 1781 (Nov 28) 1936. Smith, G. Splenectomy for Thrombocytopenic Purpura, *Brit. M. J.* **1** 157 (Jan 25) 1936. Wollstein, M., and Kreidel, K. V. Blood Picture After Splenectomy in Children, with Special Reference to Platelets, *Am. J. Dis. Child.* **51** 765 (April) 1936. Curtis, G. M., Doan, C. A., and Wiseman, B. K. Splenectomy for Hemoclastic Crises, *Ann. Surg.* **104** 892, 1936.

155 Hedenius, P., and Wilander, O. Influence of Intravenous Injections of Heparin in Man on Time of Coagulation, *Acta med. Scandinav.* **88** 443, 1936.

156 Klima, R. Ueber ein neues Behandlungsverfahren bei thrombopenischer Purpura, *Klin. Wchnschr.* **15** 935 (June 27) 1936.

157 Riolo, P. Terapia splenocontrattile endovenosa di porpore emorragiche, *Riforma med.* **52** 603 (May 2) 1936.

158 Wallgren, A. Essais de traitement du purpura thrombopénique par la phénylhydrazine, *Rev. franç. de pédiat.* **12** 370, 1936.

159 Clerc, A., Sterne, J., Delamare, J., and Paris, R. Sur les effets coagulants et hemostatiques de l'alcool octylique primaire au cours des syndromes hémorragiques, *Presse méd.* **44** 1681 (Oct 28) 1936.

160 Lowenbuig, H., and Ginsburg, T. M. Induced Hypercalcemia. Its Possible Therapeutic Relation to Thrombocytopenic Purpura, *J. A. M. A.* **106** 1779 (May 23) 1936.

Roentgen therapy has been recommended by Mettier and Stone¹⁶¹ and Rudisill¹⁶². Although they have noted improvement in many cases, they also have had many failures. Lorenz¹⁶³ has employed vitamin A to regulate splenic function. This substance was given to 20 children for two or three weeks. In some the platelets increased in number, in others there was a decrease. Similar results were observed in experiments on guinea-pigs. Lorenz expressed the belief that the increase in the thrombocyte count is due to stimulation and the decrease to the effect on the regulating system of the spleen. The reports concerning the value of vitamin C in thrombocytopenic purpura are variable. Cotti¹⁶⁴ observed both an increase and a decrease in the coagulation time in different patients. Engelkes¹⁶⁵ and Eufinger and Gaechtgens¹⁶⁶ noted beneficial effects on the capillaries only but no changes in the number of platelets. Wright and Lilienfeld¹⁶⁷ reported failures with the use of cevitic acid for purpura.

A prognostic venom test reaction for purpura has been devised by Peck, Rosenthal and Erf¹⁶⁸. One-tenth cubic centimeter of 1:3,000 dilution of standardized moccasin venom is injected intracutaneously. Saline solution is used as a control. The presence of purpuric spots within one hour at the site of the injection of the snake venom, with no reaction in the control, is interpreted as a positive result of the test. A delayed reaction may be noted within twelve hours when there is a diffusion of blood at the site of injection. Tests are carried out before and during treatment. When the test shows a negative result, improvement has been obtained. The test is used to determine whether or not splenectomy is indicated. One objection to this procedure is that in

161 Mettier, S. R., and Stone, R. S. The Effect of Roentgen Ray Irradiation on Platelet Production in Patients with Essential Thrombocytopenic Purpura Haemorrhagica, *Am J M Sc* **191** 794, 1936

162 Rudisill, H., Jr. The Successful Treatment of Essential Thrombopenia with Hemorrhage by Roentgen Rays, *J A M A* **107** 2119 (Dec 26) 1936

163 Lorenz, E. Influence of Vitamin A on Thrombocytes, *Ztschr f Kinderh* **58** 515, 1936

164 Cotti, L. Ulteriori ricerche "in vivo" sull'influenza della vitamina C sulla coagulazione del sangue, *Haematologica* **17** 483, 1936

165 Engelkes, H. Treatment of Haemorrhagic Disorders with Vitamin C, *Lancet* **2** 1285 (Dec 7) 1935

166 Eufinger, H., and Gaechtgens, G. Ueber die Einwirkung des Vitamin C auf das pathologisch veränderte weisse Blutbild, *Klin Wchnschr* **15** 150 (Feb 1) 1936

167 Wright, I. S., and Lilienfeld, A. Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitic Acid), with Special Reference to Its Effects on Capillary Fragility, *Arch Int Med* **57** 241 (Feb) 1936

168 Peck, S. M., Rosenthal, N., and Erf, L. A. The Value of the Prognostic Venom Reaction in Thrombocytopenic Purpura, *J A M A* **106** 1783 (May 23) 1936

an active state the injection of saline solution may cause damage to the capillaries, with resulting bleeding

The aforementioned authors recommended also the use of snake venom for treatment. The material is injected subcutaneously. Cambrook¹⁶⁹ stated that hot snake venom when applied locally is of great value in dental surgery to control bleeding. The value of the various types of therapy for purpura has been summarized by Tidy¹⁷⁰. Since spontaneous cure is not uncommon, a conservative attitude must be adopted concerning the value of the various therapeutic agents recommended.

HEMOPHILIA

The clinical features by which the diagnosis of hemophilia may be established have been summarized by Eley¹⁷¹. The essential findings are its inheritance, the occurrence in males, a history of repeated hemorrhages, a prolonged clotting time and a normal bleeding time. The disease is apparently transmitted according to the mendelian laws by the female. Eley cited a case in which the malady appeared in a woman whose parents were members of families in which there was hemophilia.

There is considerable diversity of opinion regarding the nature of the blood elements concerned with the clotting mechanism. Some investigators believe there is a slow disintegration of the blood platelets owing to a low thrombin and a high antithrombin content of the blood. Recently it was demonstrated by Eagle¹⁷² that there is a delay in the formation of thrombin.

The complications of hemophilia are usually the result of abnormal bleeding into the various organs and tissues of the body. Hill and Brooks¹⁷³ reported a case of Volkmann's ischemic contracture and gangrene of the fingers. Thomas¹⁷⁴ reviewed a series of 98 cases of hemophilia and pointed out that 78.5 per cent of the patients had some orthopedic involvement. Approximately 60 per cent of the patients had permanent deformities due to hemorrhages. The occurrence of hemo-

169 Cambrook, J. D. Snake Venom and Its Use in Dental Haemorrhage, *Proc Roy Soc Med* **29** 281, 1936.

170 Tidy, H. L. Treatment of Haemorrhagic Diseases, *Brit M J* **1** 850 (April 25) 1936.

171 Eley, R. C. Hemophilia, *Internat Clin* **2** 202, 1936.

172 Eagle, H. Studies on Blood Coagulation. The Rôle of Prothrombin and of Platelets in the Formation of Thrombin, *J Gen Physiol* **18** 531, 1935, Studies on Blood Coagulation. The Formation of Fibrin from Thrombin and Fibrinogen, *ibid* **18** 547, 1935, Studies on Blood Coagulation. The Nature of the Clotting Deficiency in Hemophilia, *ibid* **18** 813, 1935.

173 Hill, R. L., and Brooks, B. Volkmann's Ischemic Contracture in Hemophilia, *Ann Surg* **103** 444, 1936.

174 Thomas, H. B. Some Orthopaedic Findings in Ninety-Eight Cases of Hemophilia, *J Bone & Joint Surg* **18** 140, 1936.

philic pseudotumors involving the smaller bones and joints has been described by Firor and Woodhall¹⁷⁵ Priest¹⁷⁶ cited a case in which there was epidural hemorrhage in association with hemophilia and commented on the fact that neurologic complications are rare

At present no known specific therapy has been devised Some of the common agents employed are whole blood, citrated blood, human plasma, human and animal serum, defibrinated blood, hemostatic preparations, fibrinogen and cephalin in suspension, calcium chloride, sodium citrate, protein shock, liver and its derivatives, whole ovary and ovarian extracts and a special dietary regimen Recently, Timperley and his associates¹⁷⁷ reported excellent results in the control of hemorrhage with parenteral injections of an alcohol-acetone extract of egg white Tocantins¹⁷⁸ noted similar results with the administration of anti-platelet serum

BANTI'S DISEASE

Banti's disease was first described as a clinical entity in 1881 by the author whose name it bears The etiology was ascribed to an unidentified toxic substance which primarily affected the spleen and secondarily involved the liver The pathologic changes noted were sclerosis of the splenic vessels, atrophy of the malpighian corpuscles, induration of the pulp, sclerosis of the portal system and atrophic cirrhosis of the liver The cure was splenectomy

The existence of the disease is questioned by many investigators, and some authors¹⁷⁹ have stated that as a clinical entity it does not exist The pathologic changes which were thought by Banti to be specific have been produced experimentally in animals by obstruction of the splenic and portal veins and have been demonstrated at autopsy to be secondary to hepatic disorders or, as Rø^{179b} showed, the result of the formation of thrombi in the portal system

175 Firor, W M, and Woodhall, B Hemophilic Pseudotumor Diagnosis, Pathology and Surgical Treatment of Hemophilic Lesions in Smaller Bones and Joints, *Bull Johns Hopkins Hosp* **59** 237, 1936

176 Priest, W M Epidural Haemorrhage Due to Haemophilia Causing Compression of Spinal Cord, *Lancet* **2** 1289 (Dec 7) 1935

177 Timperley, W A, Naish, A E, and Clark, G A A New Method of Treatment in Haemophilia, *Lancet* **2** 1142 (Nov 14) 1936

178 Tocantins, L M Effets de l'injection du serum antiplaquettes a trois sujets hemophiles et a un sujet normal Action de divers serums sur le sang "in vitro," *Sang* **10** 582, 1936

179 (a) Banti's Disease, Cabot Case 21341, *New England J Med* **213** 373 (Aug 22) 1935 (b) Rø, J Stricture of Splenic Vein, Splenic Pylephlebotenosis, *Norsk mag f lægevidensk* **97** 603, 1936 (c) Rousselot, L M Role of Congestion (Portal Hypertension) in So-Called Banti's Syndrome Clinical and Pathologic Study of Thirty-One Cases with Late Results Following Splenectomy, *J A M A* **107** 1788 (Nov 28) 1936

Rousselot^{179c} reviewed 31 cases of so-called Banti's disease, in each of which splenectomy was performed. He emphasized the fact that enlargement of the spleen was the most common finding, as it was present in every instance. Other common symptoms were weakness, pain, hemorrhage, tiredness and gastro-intestinal complaints. The pathologic changes observed were the same as those which others have described and in no way differed from those seen in chronic congestion of the spleen regardless of the etiology.

The anemia present may be macrocytic or microcytic. Unquestionably microcytic anemia is due to chronic hemorrhage. Macrocytic anemia is probably the result of interference with hematopoiesis due to the failure of the liver to store or present for utilization to the bone marrow the substance necessary for the maturation of the red blood cells. Archi¹⁸⁰ stated that the increase in the diameter of the red blood cells is not associated with all hepatic disorders but occurs only with those in which there is diffuse involvement of the entire parenchyma of the liver. In his opinion the blood picture is of no prognostic significance or diagnostic value.

For several years the accepted treatment for Banti's disease has been splenectomy. A résumé of the early reports is confusing, as in many of the cases reported the condition does not fit into this syndrome. Furthermore, the disease may run a course lasting several years, so that any conclusions concerning the benefits derived from this procedure must be guarded. Rø expressed the opinion that splenectomy is of value. Others (Martin¹⁸¹ and Moore¹⁸²) have also supported this view, despite the fact that their results have not always been satisfactory or convincing. Because of the high mortality rate associated with splenectomy and the equally good results obtained with conservative measures, Goldhamer¹⁸³ suggested that the latter type of therapy is preferable.

HODGKIN'S DISEASE, LYMPHOGRANULOMA AND RELATED CONDITIONS

Lesions of the bones may be demonstrated roentgenographically in from 10 to 15 per cent of patients with Hodgkin's disease. In 3 patients Spencer and Dresser¹⁸⁴ noted a single osseous lesion, which gave rise to the predominating symptoms and simulated a primary bone tumor.

180 Archi, A. Etudes actuelles sur l'anisocytose des érythrocytes et leurs applications au diagnostic des maladies du foie, Paris méd **1** 561 (June 13) 1936.

181 Martin, L. C. Banti's Syndrome in Childhood. Report of Four Cases, Arch Dis Childhood **11** 233, 1936.

182 Moore, S. W. Portal Thrombosis Following Splenectomy for Splenic Anemia, Surg, Gynec & Obst **63** 382, 1936.

183 Goldhamer, S. M. Splenectomy in Hematopoietic Disorders. Preliminary Report, Univ Hosp Bull, Ann Arbor **2** 20, 1936.

184 Spencer, J., and Dresser, R. Lymphoblastoma (Hodgkin's and Sarcoma Type) of Bone, with Report of Three Cases Simulating Primary Malignant Tumor of Bone, New England J Med **214** 877 (April 30) 1936.

These authors¹⁸⁵ noted 120 lesions of bones in 66 cases, as follows: lumbar region of the spine, 18; dorsal region, 8; cervical region, 3; femur, 19; skull, 11; ribs, 11; sternum, 9; clavicle, 4; tibia, 4; humerus, 4; scapula, 3; os calcis, radius and maxilla, 1 each. Striking symptomatic relief, especially from pain, was obtained by roentgen therapy in small divided daily exposures of from 200 to 300 roentgens (measured in air) with total doses of from 600 to 1,200 roentgens per portal.

In Herscher's¹⁸⁶ case the major involvement was in the bone marrow, without apparent involvement of lymph nodes. The clinical course was acute, with death three months after the onset of the symptoms (weakness and backache).

Pulmonary involvement in Hodgkin's disease was noted in 37.6 per cent of 29 patients in Falconer and Leonard's¹⁸⁷ series. Five of 7 patients showed pleural effusion. Pleural lesions were present in 3 patients at autopsy.

Among the complications of lymphoblastoma which point the way to therapy, Desjardins, Haben and Watkins¹⁸⁸ enumerated fever, pruritis, discrete or diffuse infiltration of the skin, with or without pruritis, infiltration of the periorcular tissues of eyelids, with or without impairment of vision, erosion or necrosis of the sternum from enlarging mediastinal lymph nodes, pressure injury of the recurrent laryngeal nerve, pleural effusion from mediastinal obstruction, ascites from enlarged mesenteric or retroperitoneal nodes, edema of the legs from pressure on the inguinal or iliac nodes, infiltration of the testis, involvement of bone by direct erosion or invasion of bone marrow, infiltration of the spinal canal, spinal cord or brain, and secondary infection. Desjardins and his associates¹⁸⁸ warned against the use of maximal doses of x-rays and said they obtained satisfactory results with rays generated at 150 kilovolts (peak) instead of 200 kilovolts.

Certain differential features between Hodgkin's disease, lymphosarcoma and aleukemic lymphadenosis were considered in Held and Goldbloom's¹⁸⁹ study of lymphadenopathy.

185 Dresser, R., and Spencer, J. Hodgkin's Disease and Allied Conditions of Bone, *Am J Roentgenol* **36** 809, 1936.

186 Herscher, H. Hodgkin's Disease of Bone Marrow and Liver Without Apparent Involvement of Lymph Nodes, *Am J Roentgenol* **35** 73, 1936.

187 Falconer, E. H., and Leonard, M. E. Hodgkin's Disease of the Lung, *Am J M Sc* **191** 780, 1936.

188 Desjardins, A. U., Haben, H. C., and Watkins, C. H. Unusual Complications of Lymphoblastoma and Their Radiation Treatment, *Am J Roentgenol* **36** 169, 1936.

189 Held, I. W., and Goldbloom, A. A. Adenopathy. Discussion of Differential Diagnosis Between Hodgkin's Disease, Lymphosarcoma and Aleukemic Lymphadenosis, *Internat Clin* **3** 70, 1936.

In studying patients with Hodgkin's disease, Rosenthal¹⁹⁰ found that those in whom there was a predominance of lymphocytes in the glands showed an average duration of life after the onset of the disease of four and thirty-five hundredths years, those in whom the lymphocytes were moderately reduced, two and twenty-nine hundredths years, and those in whom the lymphocytes were practically absent, one and fourteen hundredths years. A progressive disappearance of lymphocytes characterizes the disease, whether roentgen therapy is used or not. In Raagaard's¹⁹¹ series of 12 male and 7 female patients the average duration was about sixteen months (one to sixty-four months). He found that in a patient who had had the disease for six years repeated recurrences in the mediastinum were always alleviated by irradiation, which did not appear to decrease in effectiveness.

Watt,¹⁹² in a study of 201 cases of Hodgkin's disease over a decade, recommended high voltage roentgen therapy spread over a period of from a week to a month. Recrudescences are to be treated at the earliest possible moment. Pyrexia is usually associated with an active focus. Arsenic should not be used for six weeks after roentgen therapy. Periodic inspection of patients is advisable.

That syphilis may simulate Hodgkin's disease clinically was noted by Clodfelter.¹⁹³

In Chevallier and Gorse's¹⁹⁴ patient tuberculosis of the lymph nodes was first noted, but three years later Hodgkin's disease had developed. There was a good response to roentgen therapy. In Funshteyn's¹⁹⁵ patient also there was a combination of the two diseases. The patient reported on by Hernández, Yrigoyen and Guastavino's¹⁹⁶ showed generalized lymphogranulomatosis, with the lesions simulating tuberculosis of the lung, pleura and lymph nodes.

The localization of lymphogranuloma may give rise to specific symptoms as well as cause confusion in diagnosis, as when nodules or cavity

190 Rosenthal, S. R. Significance of Tissue Lymphocytes in Prognosis of Lymphogranulomatosis, *Arch Path* **21** 628 (May) 1936.

191 Raagaard, O. Nineteen Cases of Lymphogranulomatosis (Sternberg), *Ugeskr f læger* **98** 759 (Aug 13) 1936.

192 Watt, W. L. Hodgkin's Disease and Deep X-Ray Therapy, *Brit M J* **2** 712 (Oct 10) 1936.

193 Clodfelter, H. M. Syphilis Presenting Clinical Picture of Hodgkin's Disease, *Arch Dermat & Syph* **33** 535 (March) 1936.

194 Chevallier, P., and Gorse, J. *Maladie de Hodgkin ayant commencé par une adenopathie tuberculeuse du cou*, *Sang* **10** 894, 1936.

195 Funshteyn, L. Lymphogranulomatose und Tuberkulose. *Klinische Untersuchung*, *Beitr z Klin d Tuberk* **88** 41, 1936.

196 Hernández, I. M., Yrigoyen, L., and Guastavino, C. R. Pseudo tuberculosis ganglio-pleuro-pulmonar por granulomatosis generalizada, *Arch de fisiol* **12** 21, 1936.

formation appears in the lungs. The bone lesions may be osteoclastic or osteoblastic and sclerosing, with periosteal osseous formations. A new sign of unfavorable progress is a peculiar faint transparent complexion with red cheeks in a patient with multiple lymphomas. For treatment, a single dose of from 100 to 200 roentgens is given every day or every other day until from 1,000 to 1,400 roentgens have been given over the glands, lungs, spleen and bone lesions (Ebbehøj¹⁹⁷).

Lymphosarcoma, or Hodgkin's disease, may first appear in the abdominal, mediastinal or inguinal nodes rather than primarily in the neck, with subsequent spread to other regions. Symptoms of abdominal lymphomatosis are nausea, vomiting, increasing constipation and distention with gas. Pain may be in the back or sides or legs, with obstructive edema. Fever and pruritis are important symptoms. Maximum doses of roentgen rays are to be avoided, and the highest kilovoltage is not necessarily desirable. Desjardins and Watkins¹⁹⁸ recommended repeated treatment at regular intervals of three or four weeks, unless pronounced leukopenia contraindicates this course.

From a study of cases and reviews of published data Ginsburg¹⁹⁹ was unable to find clearcut criteria for the absolute differentiation of Hodgkin's disease and lymphosarcoma. "Hodgkin's disease," he summarized, "varies in no fundamental clinical characteristics from lymphosarcoma. Whatever clinical variations it may present at times are merely variations that one may encounter in any disease affecting different individuals under different constitutional and environmental conditions."

Chapman,²⁰⁰ on the other hand, on the basis of Gordon's test, expressed the belief that Hodgkin's disease is a separate clinical and pathologic entity, distinct from lymphosarcoma, reticulum cell sarcoma, giant follicular lymphoma and lymphoblastoma of undetermined types. Gordon's test, which consists of the intracerebral injection into rabbits of a saline emulsion of Hodgkin's tissue, and the observation for ataxia, spasm and paralysis, gave negative results in 64 of 65 controls. In 9 of 16 cases of Hodgkin's disease at least 1 rabbit gave a positive reaction, although 1 or more rabbits failed to give a reaction in 5 of the 9

197 Ebbehøj, K. Lymphogranulomatosis, *Hospitaltid* **79** 253 (March 17) 1936

198 Desjardins, A. U., and Watkins, C. H. Abdominal Lymphoblastoma and Its Treatment by Irradiation, *South M J* **29** 344, 1936

199 Ginsburg, S. Lymphosarcoma and Hodgkin's Disease. Clinical Characteristics, *Ann Int Med* **10** 337, 1936

200 Chapman, Earle M. Studies in Hodgkin's Disease. Clinical Application of the Gordon Test (a Syndrome of Ataxia, Spasm and Paralysis Induced in Rabbits by the Intracerebral Injection of Emulsified Hodgkin's Tissue), *Ann Int Med* **10** 742, 1936

The test then shows some specificity for Hodgkin's disease but is not always correct in known cases

Applying Gordon's test, Goldstein²⁰¹ obtained positive responses with material from nine lymphogranulomatous nodes. In the two tests which gave negative results, both in established cases of Hodgkin's disease, all inoculated animals remained free from the encephalitic syndrome. All control groups (twenty, including five tuberculous glands and two from patients with infectious mononucleosis) gave negative results.

For diagnosis Emile Weil, Isch-Wall and Perlès²⁰² used lymph gland puncture. Endothelial elements and giant cells of Steinberg are diagnostic features. In some types there is an increase in the number of monocytes or eosinophils or massive infiltration with polymorphonuclear cells. In the advanced stages fibrous tissue predominates.

Sailer²⁰³ studied Hodgkin's disease in a man aged 77 years and noted that the disease did not differ essentially from that in younger patients.

Jorg²⁰⁴ summarized the general pathologic picture of Hodgkin's disease and reviewed the recent literature on the subject.

Gordon's test for Hodgkin's disease gave positive results in 2 cases in Rosenberg and Bloch's²⁰⁵ series during early stages, but negative results in a case of chronic involvement of a year's duration. These authors described the technic and reviewed the literature on the subject. When a positive result is obtained the rabbits into which the gland emulsion has been injected intracerebrally show symptoms after an incubation period of from two to six days (maximum, sixteen days). Ataxia, staggering, falling, retraction of the head, opisthotonos, convulsive movements, nystagmus, grinding of the teeth, urinary and fecal incontinence, progressive wasting and weakness affecting particularly the hind quarters. Death may follow in from three days to a month, or recovery or a chronic state may supervene.

Injection of saline emulsions of glands involved by Hodgkin's disease into the lymphatic glands of the paws of dogs did not cause the

201 Goldstein, J. D. The "Gordon Test" for Hodgkin's Disease, *Am J M Sc* **191** 775, 1936.

202 Weil, P. E., Isch-Wall, P., and Perlès, S. Le diagnostic de la maladie de Hodgkin par la ponction des ganglions, *Bull et mém Soc med d hôp de Paris* **52** 1006 (June 22) 1936, *Presse med* **44** 1540 (Oct 3) 1936.

203 Sailer, S. Hodgkin's Disease in the Aged, *Am J Clin Path* **6**:241, 1936.

204 Jorg, M. E. La anatomía patológica general de la granulomatosis maligna de Hogkin-Paltauf y Sternberg (conceptos actuales, nueva bibliografía), *Semana med* **1** 1741 (June 4) 1936.

205 Rosenberg, D. H., and Bloch, L. The Gordon Test for Hodgkin's Disease, *J A M A* **106** 1156 (April 4) 1936.

development of the disease after from seven months to three years (Chapman ²⁰⁶)

Slight leukocytosis was noted by Roth and Watkins ²⁰⁷ in cases of Hodgkin's disease of between one and two years' duration. Polymorphonuclear neutrophils were slightly increased in number after six months, with a slight relative decrease in the number of lymphocytes. Monocytes tend to be more mature than in the average normal person. These tendencies are not more marked when there is extensive involvement of the body. The author concluded "There is no specific change in the blood picture which is diagnostic of Hodgkin's disease."

Wiseman ²⁰⁸ claimed that the majority of patients with Hodgkin's disease have a normal or low leukocyte count. There is a tendency to neutrophilia (5,000 or more neutrophils per cubic millimeter), at least two thirds of his patients showed no increase in the number of eosinophils. Definite lymphopenia was characteristic (less than 1,500 lymphocytes per cubic millimeter), with monocytosis (700 monocytes per cubic millimeter), giving a high monocyte-lymphocyte ratio (1:33).

Peirce, Jacox and Hildreth ²⁰⁹ studied the records of 214 patients with Hodgkin's disease and noted that the clinical symptoms and signs and the changes in the character of the blood often suggest the disease. They are not indicative of the extent of the intrathoracic involvement. In two thirds of the patients roentgen examination of the chest revealed the diagnosis and extent of the disease.

From a survey of the clinical results of roentgen treatment of 161 patients with Hodgkin's disease, Jacox, Peirce and Hildreth ²¹⁰ concluded that this type of therapy induced definite extension of life as compared with the results for patients who did not receive this treatment. "Systemic irradiation," they said, "has been no more effectual than repeated local irradiation in prolongation of the total duration of the disease in those cases now known to have died." They advocated systemic irradiation of all lymphatic areas.

206 Chapman, E. M. Studies in Hodgkin's Disease. Unsuccessful Experiments to Transmit Hodgkin's Disease to Dogs by Intralymphatic Injection, *Proc Soc Exper Biol & Med* **33** 572, 1936.

207 Roth, G. M., and Watkins, C. H. The Leukocyte Picture in Hodgkin's Disease, *Ann Int Med* **9** 1365, 1936, *Proc Staff Meet, Mayo Clin* **11** 593 (Sept 16) 1936.

208 Wiseman, B. K. Lymphopoiesis, Lymphatic Hyperplasia, and Lymphemia. Fundamental Observations Concerning the Pathologic Physiology and Interrelationships of Lymphatic Leukemia, Leukosarcoma and Lymphosarcoma, *Ann Int Med* **9** 1303, 1936.

209 Peirce, C. B., Jacox, H. W., and Hildreth, R. C. Roentgenologic Considerations of Lymphoblastoma. Roentgen Pulmonary Pathology of the Hodgkin's Type, *Am J Roentgenol* **36** 145, 1936.

210 Jacox, H. W., Peirce, C. B., and Hildreth, R. C. Roentgenologic Considerations of Lymphoblastoma. Roentgen Therapy of Hodgkin's Disease, *Am J Roentgenol* **36** 165, 1936.

The survival period after roentgen therapy in O'Brien's²¹¹ series averaged fourteen and two-fifths months. Anemia is a greater source of potential danger after teleoroentgen therapy than after local treatment. O'Brien stated

The obvious direct benefits from roentgen therapy are decrease in the size of the liver and spleen, with consequent relief from pressure symptoms, resorption of pleural effusion, resorption of ascites, relief of pain, restoration of sensibility of locomotion in cord and vertebral metastases, increase in red cells and color index, remissions of the disease with return to occupation, and comparative comfort over long periods of time.

Lymphosarcoma of the intestine usually does not cause constriction but more often produces sacculations. In Greenfield's²¹² case the diagnosis was made preoperatively on the basis of the roentgenographic changes. After high voltage roentgen therapy an excellent remission was produced.

Various aspects of Hodgkin's disease and related diseases have been emphasized in recent reports: cutaneous involvement (Arzt²¹³), involvement of the scalp (Wrong²¹⁴), involvement of the orbit (Kyrieleis²¹⁵ and Muscatello²¹⁶), primary localization in the nasopharynx (Berendes²¹⁷), elephantiasis of the penis and scrotum (Sánchez-Covisa and de la Cuesta²¹⁸), hemolytic jaundice (Fortunato²¹⁹), localization in the thyroid region simulating thyroid adenoma (Presno y Bastiony²²⁰), localization in the mediastinum (Medoc and Marcos²²¹) and primary involvement of the tonsil (Wullstein²²²).

211 O'Brien, F. W. Roentgen Treatment of the So-Called Malignant Lymphomas, *J. A. M. A.* **107** 2022 (Dec 19) 1936.

212 Greenfield, H. Early Roentgen Diagnosis of Jejunal Lymphosarcoma. Report of Case, *Am. J. Roentgenol.* **36** 674, 1936.

213 Arzt, L. Zur Kenntnis der Lymphogranulomatosis cutis (Paltauf-Sternberg), *Wien. med. Wchnschr.* **86** 677 (June 20) 1936.

214 Wrong, N. M. Hodgkin's Disease of the Scalp. Report of a Case, *Arch. Dermat. & Syph.* **33** 259 (Feb.) 1936.

215 Kyrieleis, W. Ueber Augenhintergrundsveränderungen bei Lymphogranulomatose, *Ztschr. f. Augenh.* **89** 193, 1936.

216 Muscatello, F. Lipogranulomatosi dell' orbita, *Rassegna ital. d'ottal.* **5** 108, 1936.

217 Berendes, J. Der Epipharynx als primärer Sitz der Lymphogranulomatose, *Arch. f. Ohren-, Nasen- u. Kehlkopfh.* **141** 141, 1936.

218 Sánchez-Covisa, J., and de la Cuesta, L. Elefantiasis peneoesrotal en el curso de linfogranulomatosis maligna de Paltauf-Sternberg, *Actas dermo-sif.* **28** 734 (May) 1936.

219 Fortunato, A. Morbo di Hodgkin con ittero emolitico, *Studium* **26** 147 (July 1) 1936.

220 Presno y Bastiony, J. A. Enfermedad de Hodgkin de localización primitiva en la región tiroidea simulando un bocio, *Rev. de med. y cir. de la Habana* **41** 213 (April 30) 1936.

Gordon ²²³ and Warner ²²⁴ experimented with vaccine therapy for Hodgkin's disease

LEUKEMIA

The outpouring of immature cells of all types in leukemia was shown in the cases of 2 patients characterized by Campbell, Henderson and Croom ²²⁵ as demonstrating a mixed monocytic-myeloid reaction. While the monocytes predominated in the blood, both monocyte and myeloid cells were present in the tissues in about equal proportions. The process was interpreted as a "stem cell" hyperplasia with simultaneous differentiation into two distinct cell types. Both patients showed necrotic ulceration at the anorectal region, and 1 showed a localized tumor in the cecum and appendix.

The coincidental occurrence in the same patient of pernicious anemia (macrocytosis, reticulocyte response to liver extract, achlorhydria, reduced gastric secretion, loss of vibratory sense and degeneration of the posterior and lateral columns of the spinal cord) and of lymphatic leukemia (splenomegaly, lymphadenopathy and leukocytosis—330,000 leukocytes per cubic millimeter, with a predominance of lymphocytes) has been reported by Rich and Schiff ²²⁶. A somewhat similar situation was presented by Duthoit and Houcke's ²²⁷ patient with "subleukemic lymphatic leukemia" and a myeloid reaction, with megaloblasts and a color index of 1.34.

Krumbhaar ²²⁸ suggested the term lymphomatoid diseases for the heterogeneous group of conditions classified as lymphoblastoma, limiting the latter term to "a tumor derived from the lymphoblast." In comparing the weight of the spleen in different types of leukemia, the average was as follows: acute lymphatic, 693.5 Gm.; chronic lymphatic

221 Medoc, J., and Marcos, J. R. Un caso de linfogranulomatosis solitaria del mediastino, estudio clinico y anatomopatologico, *An. Fac. de med. de Montevideo* **20** 319, 1935.

222 Wullstein, H. Ueber beginnende Lymphogranulomatose mit Primarin-fekt an der Gaumenmandel und ihre Behandlung, *Arch. f. Ohren-, Nasen- u. Kehlkopfheilk.* **141** 146, 1936.

223 Gordon, M. H. Aetiology of Lymphadenoma. Sensitized Vaccine of Elementary Bodies, *Lancet* **2** 65 (July 11) 1936.

224 Warner, E. C. Treatment of Lymphadenoma, with Sensitized Vaccine of Elementary Bodies, *Lancet* **2** 417 (Aug. 22) 1936.

225 Campbell, A. C. P., Henderson, J. L., and Croom, J. H. Monocytic Leukaemia with Myeloid Hyperplasia and Localised Tumour Formation, *J. Path. & Bact.* **42** 617, 1936.

226 Rich, M. L., and Schiff, L. A Case of Pernicious Anemia and Chronic Lymphatic Leukemia, *Ann. Int. Med.* **10** 252, 1936.

227 Duthoit, A., and Houcke, E. Subleucemie lymphoïde avec anemie megaloblastique et reaction myeloïde, *Sang.* **10** 252, 1936.

228 Krumbhaar, E. B. The Lymphomatoid Diseases (the So-Called Lymphoblastomas), *J. A. M. A.* **106** 286 (Jan. 25) 1936.

1,297.5 Gm, acute myelogenous, 482.2 Gm, and chronic myelogenous, 1,879.2 Gm. Among the patients with myelogenous leukemia, spleens weighing from 4,930 and 5,380 Gm were encountered, and among the patients with lymphatic leukemia there was one of 4,400 Gm.

A case of acute leukemia which first became manifest after treatment with a radio-active solution has been described by Rimbaud, Anselme-Martin, Lafon and Castagne.²²⁹ Reports of cases emphasizing involvement of the liver and spleen (Cabot case 22,282²³⁰) as well as absence of splenomegaly (Legrand²³¹) have been published. Marcus²³² described the case of a patient who had a long remission in the course of acute aleukemic leukemia. In Zemplen's²³³ patient the disease started as acute myeloblastic leukemia and developed into chloroma. Cutaneous involvement was noted in a patient by Goldhamer and Barney,²³⁴ and they reviewed the findings in 16 other similar cases reported in the literature. The appearance of cutaneous nodular infiltrations suggests a bad prognosis, as death followed in from fifteen days to four months in this group. The nodules vary in diameter from about 2 to 20 mm, and the color is that of normal skin or various depths of purple. The most common sites are the skin of the trunk, the anterior surface of the chest, the extremities and rarely the face and mucous membranes. Zimmerman and Curtis²³⁵ described the cutaneous nodules of a patient with myelogenous leukemia which progressed to the blast stage after leukopenia was induced by intensive roentgen therapy.

The problem of the differential diagnosis of marked eosinophilia and eosinophilic leukemia was presented in a case described by Lottrup.²³⁶ The leukocyte count was 13,800 per cubic millimeter, with 54 per cent eosinophils. The diagnosis of eosinophilic bronchitis was made rather than leukemia, because of the sparsity of immature forms.

229 Rimbaud, L., Anselme-Martin, G., Lafon, R., and Castagné, R. Leucémie aigue en concomitance avec un traitement radio-actif suivi sans contrôle médical, *Arch Soc d sc med et biol de Montpellier* **17** 118, 1936.

230 Aleukemic Myeloid Leukemia with Involvement of Liver and Spleen, Cabot Case 22282, *New England J Med* **215** 91 (July 9) 1936.

231 Legrand, R. Leucémie myeloïde sans splénomégalie, *Echo med du Nord* **5** 858 (May 24) 1936.

232 Marcus, I. H. Complete Temporary Recovery of Long Duration, in Acute Aleukemic Myeloid Leukemia. Case Report, *J Lab & Clin Med* **21** 1006, 1936.

233 Zemplen, B. Ein im Bilde einer akuten Myeloblasten-Leukämie beginnendes Chlorom, *Folia haemat* **55** 262, 1936.

234 Goldhamer, S. M., and Barney, B. F. Myelogenous Leukemia with Cutaneous Involvement, *J A M A* **107** 1041 (Sept 26) 1936.

235 Zimmerman, E. F., and Curtis, H. C. Aleukemic Myelosis with Cutaneous Nodules, *Arch Dermat & Syph* **33** 684 (April) 1936.

236 Lottrup, M. C. Hochgradige Eosinophilie und eosinophile Leukämie, *Folia haemat* **54** 66, 1935.

Among the less common types of leukemia is an example of an acute basophilic form described by Groat, Wyatt, Zimmer and Field²³⁷. Their patient had a leukocyte count varying from 40,000 to 121,000 per cubic millimeter, with basophils constituting from 21 to 61 per cent of the cells. There were progressive anemia, thrombopenia and abnormal platelets. The sternal bone marrow showed many basophils, with immature forms, although the neutrophils were apparently normal. There was a progressive increase in the number of myeloblasts (24,000). Roentgen therapy was of help early in the disease. Symptomatic improvement followed blood transfusions. The total duration of the disease was about eight months, with death from bronchopneumonia. Duodenal ulcers complicated the picture.

A second unusual type was noted by Patek and Castle²³⁸ in a woman of 60 years who showed plasma cell leukemia. Eleven similar cases were noted in the literature. The leukocyte count varied from 21,800 to 50,100 per cubic millimeter, with from 27 to 43 per cent of the cells belonging to the plasma cell group. There was progressive anemia, and death resulted from bronchopneumonia. The pathologic picture of this condition has been described by Jores and Bruns,²³⁹ who characterized the lesion as malignant plasmoma. In this patient, a 64 year old woman, the leukocyte count rose to 38,000 per cubic millimeter, with 45 per cent plasma cells. There was a multiple myeloma made up of plasma cells.

Additional cases of megakaryocytic leukemia (an aleukemic form with enlargement of the liver and spleen) have been recorded by Chini,²⁴⁰ Emile Weil, Isch-Wall, Perlès and Scemama²⁴¹ and Introzzi.²⁴²

A case of myelogenous leukemia in a woman with a red blood cell count of 5,500,000, a leukocyte count of from 22,000 to 33,000 and a platelet count of more than 2,500,000 per cubic millimeter was reported by Drake²⁴³. In discussing this case Dameshek²⁴⁴ said that the diagnosis should have been polycythemia, as he has noted high platelet counts

237 Groat, W. A., Wyatt, T. C., Zimmer, S. M., and Field, R. E. Acute Basophilic Leukemia, *Am J M Sc* **191** 457, 1936

238 Patek, A. J., Jr., and Castle, W. B. Plasma Cell Leukemia. Consideration of the Literature with Report of a Case, *Am J M Sc* **191** 788, 1936

239 Jores, A., and Bruns, W. Ein Fall von "malignem Plasmom" mit einem Beitrag zur sog. "Plasmazellenleukämie," *Folia haemat* **55** 227, 1936

240 Chini, V. La mielosi aleucemica megacariocitaria, *Policlinico (sez. med.)* **43** 257, 1936

241 Weil, P. E., Isch-Wall, P., Perlès, S., and Scemama, J. Un cas de splénomégalie myéloïde mégacaryocytaire, *Sang* **10** 797, 1936

242 Introzzi, P. Contributo allo studio della patologia del sistema megacariocitico (megacariociti nel sangue periferico di anemia perniziosa progressiva di leucemia acuta emocitoblastica), *Haematologica* **16** 217, 1935

243 Drake, C. B. Leukemia with Thrombocytosis, *J A M A* **106** 1005, (March 21) 1936, **107** 446 (Aug. 8) 1936

244 Dameshek, W. Leukemia or Polycythemia, *J A M A* **106** 1837 (May 23) 1936

in that disease Kugelmass²⁴⁵ claimed that in this case it was not justifiable to make a diagnosis of latent leukemia on the basis of a high platelet count alone, as secondary thrombocythemia may be present in polycythemia, lymphogranulomatosis, chronic myelosis, splenic dysfunction and injury to the tissues by severe infection or surgical trauma. Subsequent study confirmed the diagnosis of leukemia. The case is interesting as it brings out many difficulties in the diagnosis of conditions in which intensive stimulation of the bone marrow is a factor.

Hyperproteinemia and hypereuglobulinemia with the secretion of Bence-Jones' protein in the urine characterized Keilhack's²⁴⁶ case of aleukemic myelogenous leukemia. A relationship to the myelomas was suggested, and other diseases in which these symptoms appear were analyzed.

The fever in leukemia, according to Vlados,²⁴⁷ is the result of the disturbed purine metabolism.

In acute "blast" leukemia (lymphatic) Arneth²⁴⁸ noted a relative predominance of oval blood platelets, 2.5 microns in diameter, with an absolute decrease in the number of larger and of elongated forms. This tendency was less marked in cases of chronic lymphatic leukemia.

Hepatic infarction may be a complication of chronic myelogenous leukemia (Morgan, Lieber and Stewart²⁴⁹).

Leukemic cells from old mice have a lower rate of metabolism than those from younger mice. When cells from either group were inoculated into the other, the resulting leukemic cells assumed a rate more nearly comparable to the age of the host. "Host age," commented Victor and Potter,²⁵⁰ "does not modify the inherent constitution of the leukemia cells but acts as a determining environmental factor on their metabolism."

In a strain of pure albino rats Wilens and Sproul²⁵¹ noted the spontaneous development of leukemia in 3.3 per cent of the animals (myeloid, 7 cases, chloromyeloid, 4 cases, and lymphatic, 1 case). The

245 Kugelmass, I. N. Leukemia with Thrombocytosis, *J. A. M. A.* **106** 1588 (May 2) 1936.

246 Keilhack, H. Die Hyperproteinämie und Hypereuglobulinämie als Symptome einer chronischen aleukamischen Myelose, *Folia haemat.* **55** 406, 1936.

247 Vlados, C. Sur la genèse de l'état fébrile chez les malades atteints de leucémie, *Sang.* **9** 961, 1935.

248 Arneth, J. Ueber das qualitative Thrombocytenblutbild bei der lymphatisch-leukamischen Reaktion (Leukämie) auf Grund von 30 Beobachtungen, *Folia haemat.* **56** 49, 1936.

249 Morgan, D. R., Lieber, M. M., and Stewart, H. L. Hepatic Infarction in Myelogenous Leukemia and Periarteritis Nodosa, *Am. J. M. Sc.* **192** 540, 1936.

250 Victor, J., and Potter, J. S. Host Age and Cell Metabolism in Mouse Lymphatic Leukemia, *Proc. Soc. Exper. Biol. & Med.* **33** 609, 1936.

251 Wilens, S. L., and Sproul, E. E. Spontaneous Leukemia and Chloroleukemia in the Rat, *Am. J. Path.* **12** 249, 1936.

ages varied from 18 months to 2 years. There were 8 males and 4 females. In the rats with chloroleukemia the tumors were greenish, the pigment resembling that of human beings with chloroma.

Wiseman²⁰⁸ concluded that lymphatic leukemia may be either neoplastic or metabolic, in the majority of cases chronic lymphatic leukemia is of the latter type. The metabolic derangement was postulated as being similar to the mechanism which produces pernicious anemia. Wiseman, Doan and Erf²⁵² claimed that the anemia in lymphatic leukemia is due not to the crowding out of erythroblastic tissue from the marrow but to an effect of increased volume of lymphatic tissue elsewhere in the body. Myelopoiesis, they concluded, is metastatic when it occurs in lymph nodes. Myeloid or lymphoid hyperplasia occurs at the expense of the hypoplasia of the other.

To support the theory of the local origin of hemocytoblastic growths, as opposed to the metastatic concept, Smith and Silberberg²⁵³ presented a patient with multiple myeloma in whom there were undifferentiated or partly differentiated blood cells (proerythroblasts and other immature red blood cells, lymphocytes, plasma cells and megakaryocytes).

Articular manifestations in leukemia are not uncommon (Krafft²⁵⁴), and the syndrome may simulate acute rheumatism and Still's disease (Conybeare²⁵⁵). Erythroderma was the initial and, for a time, the only clinical manifestation of subacute leukemia (blast) in a patient described by Margarot, Rimbud and Roche²⁵⁶.

Rigler²⁵⁷ reported the appearance of "enormously enlarged gastric rugae, resembling the convolutions of the brain" in a patient with a basal cell carcinoma of the skin and leukemic infiltration of a cervical lymph node and of the skin. The blood was not abnormal. Improvement followed roentgen therapy. The roentgenographic appearance of the stomach is not specific, however, but may be similar to that seen in chronic hypertrophic gastritis. The latter condition is not improved by roentgen therapy.

252 Wiseman, B. K., Doan, C. A., and Erf, L. A. A Fundamental Reciprocal Relationship Between Myeloid and Lymphoid Tissues. Its Recognition, Nature, and Importance as Revealed by Experimental and Clinical Studies, *J. A. M. A.* **106** 609 (Feb. 22) 1936.

253 Smith, R. P., and Silberberg, M. Multiple Myeloma of Hemocytoblastic Type, *Arch. Path.* **21** 578 (May) 1936.

254 Krafft, J. Leukämische Gelenksymptome im Kindesalter, *Kinderarztl. Praxis* **7** 295 (July) 1936.

255 Conybeare, E. T. Case of Leukaemia Simulating Acute Rheumatism and Still's Disease, *Guy's Hosp. Rep.* **86** 343, 1936.

256 Margarot, J., Rimbaud, P., and Roche, J. Erythrodermie constituant la manifestation clinique initiale et pendant quelque temps, exclusive d'une leucémie à éléments primordiaux et d'évolution subaiguë, *Bull. Soc. franç. de dermat. et syph.* (Reunion dermat., Lyon) **42** 1503, 1935.

257 Rigler, L. G. Leukemia of the Stomach Producing Hypertrophy of the Gastric Mucosa, *J. A. M. A.* **107** 2025 (Dec. 19) 1936.

The nucleotide nitrogen content of the blood of patients with leukemia is high. For normal males the amount is 6.2 mg and for females 5.2 mg per hundred cubic centimeters. The average for 10 males with myelogenous leukemia with an elevated leukocyte count was 7.36 mg and for 5 females 5.84 mg per hundred cubic centimeters. In normal persons and in patients with aleukemic leukemia the nucleotide nitrogen is more closely correlated with the red blood cell count (Allen, Lucia and Eiler ²⁵⁸).

Certain chemical differences in the composition of the white blood cells in leukemia, especially in the lipid fraction, were noted by Boyd ²⁵⁹. In 9 patients with chronic myelogenous leukemia the values for total lipids, total fatty acids, total cholesterol, free cholesterol and phospholipid were greater than normal, as compared with the condition in 8 patients with chronic lymphatic leukemia, for whom the amounts were less than normal. The amount of neutral fat was slightly increased in lymphatic leukemia, but in both types the ester cholesterol content was less than normal. In a patient with "acute myeloid leukemia" the leukocyte lipid content was relatively low, whereas in 2 patients with Hodgkin's disease it was relatively high.

Fiessinger and Laur ²⁶⁰ reported that they had under their care a 51 year old patient known to have had lymphatic leukemia for twenty years. He had had roentgen therapy at times. The blood was going into the blast stage, with a leukocyte count of 208,000 per cubic millimeter.

The occurrence of localized leukemic infiltrations was pointed out by Cleland,²⁶¹ and the resemblance to lymphosarcoma and pseudo-leukemia was noted. Patients with infiltration in the cardiac muscle, kidneys, pancreas, brain and other organs were cited, showing the specific symptomatology which these tumors may cause.

Craver ²⁶² commented on the great variation and severity of symptoms in different patients with leukemia. A long duration is more common in lymphatic than in myelogenous leukemia. There are certain features which suggest a relationship between leukemia and Hodgkin's disease, lymphosarcoma and erythremia. Lymphosarcoma may terminate with a leukemic syndrome, as noted in the patient of Morin,

²⁵⁸ Allen, F. W., Lucia, S. P., and Eiler, J. J. Nucleotide Nitrogen Content of Pathologic Human Whole Blood, *J. Clin. Investigation* **15** 157, 1936.

²⁵⁹ Boyd, E. M. The Lipid Composition of the White Blood Cells in Leukemia, *Arch. Path.* **21** 739 (June) 1936.

²⁶⁰ Fiessinger, N., and Laur, C. M. Leucémie lymphatique splénique pure d'une durée de 20 ans et encore en traitement, *Sang* **10** 743, 1936.

²⁶¹ Cleland, J. B. Leukaemic Infiltrations, *Brit. M. J.* **2** 1191 (Dec. 21) 1935.

²⁶² Craver, L. F. Clinical Manifestations and Treatment of Leukemia, *Am. J. Cancer* **26** 124, 1936.

Lemieux and Leblond ²⁶³ Lymphosarcoma of the mediastinum was the primary clinical lesion Wiseman ²⁶⁴ also discussed this phase of lymphosarcoma

A detailed account of a patient with chronic myelogenous leukemia and painful priapism was given by Denechau ²⁶⁵ This complication, although frequently mentioned in accounts of leukemia, is relatively rare In this case there was improvement after intensive irradiation over the pelvis and spleen

In a patient with lymphatic leukemia, severe leukopenia (200 to 800 leukocytes per cubic millimeter) developed after roentgen therapy The initial white blood cell count was 70,200 per cubic millimeter The patient received nine treatments within thirty-five days, totaling probably more than 5,500 roentgens, over different parts of the body The polymorphonuclear leukocyte count was reduced to 5 per cent ("agranulocytosis") After therapy with pentose nucleotide, Fiessinger and Boudin ²⁶⁶ found an increase in the total leukocyte count, with a slight increase in the number of polymorphonuclears Death followed in two months

Lazeanu and Saragea ²⁶⁷ studied a patient with chronic lymphatic leukemia for whom the leukocyte count was 2,500,000 per cubic millimeter, over 96 per cent of the cells being lymphocytes The count was reduced to 1,000,000 per cubic millimeter with roentgen therapy (Other authors have reported counts of from 1,500,000 to 2,000,000 per cubic millimeter)

The basal metabolic rate parallels the clinical condition of the patient more closely than the blood count, although this is not infallible, concluded Middleton, Meyer and Pohle ²⁶⁸ from a careful study of 21 patients with leukemia

The coincidental occurrence of carcinoma (cutaneous) and lymphatic leukemia in the same patient has been described by Pulvertaft ²⁶⁹ He

263 Morin, E, Lemieux, R, and Leblond, S Syndrome leucémique au cours d'un lymphosarcome du médiastin, *Laval med* **1** 24, 1936

264 Wiseman, B K The Blood Pictures in the Primary Diseases of the Lymphatic System Their Character and Significance, *J A M A* **107** 2016 (Dec 19) 1936

265 Denechau, D Un nouveau cas de priapisme révélateur d'une leucémie myéloïde Résultats heureux et prolongés du traitement radiothérapique, *Sang* **10** 86, 1936

266 Fiessinger, N, and Boudin, G Aleucie hémorragique et agranulocytose après un traitement radiothérapique, au cours d'une leucémie lymphoïde splénomégalique, *Sang* **10** 377, 1936

267 Lazeanu, E, and Saragea, T Leucémie lymphatique avec un très grand nombre de leucocytes dans le sang, *Sang* **10** 123, 1936

268 Middleton, W S, Meyer, O O, and Pohle, E A Influence of Roentgen Therapy upon Basal Metabolism in Leukemia, *Radiology* **26** 586, 1936

269 Pulvertaft, R J V Multiple Primary Epithelioma in Lymphatic Leukaemia, *Brit J Surg* **24** 50, 1936

commented on the fact that lymphocytes have been considered as a protective barrier against the spread of tumors. Similarly, a patient may have military tuberculosis and leukemia (Harbitz²⁷⁰). It is suggestive that the leukemic cell differs in its functional possibilities from the normal lymphocyte.

From a study of patients with acute leukemia Jaffé²⁷¹ emphasized the excessive destruction of blood in some patients, with a compensatory reactive myelopoiesis. This results in the production of an increasing number of immature precursors of blood cells until the hemocytoblastic stage is reached.

Neumann and Neugebauer²⁷² described experiences in the giving of transfusions to leukemic patients which others no doubt have had. They noted the occurrence of reactions if the identical type of blood was not used, blood from group O donors causing reactions and hemolysis in all patients except those whose blood belonged to the same group.

Monocytic Leukemia—Chini²⁷³ described a patient showing a syndrome which is encountered occasionally among patients with pernicious anemia. His patient had a blood picture of pernicious anemia which later changed into that of monocytic leukemia. Splenomegaly was present, and marked megakaryocytosis was noted in the spleen. Kato²⁷⁴ described a case of monocytic leukemia in an 18 month old infant.

Monocytic leukemia is described by some as a reticulo-endotheliosis (Reich²⁷⁵), acute histiocytic leukemia (Ramsey and Tank²⁷⁶) and aleukemic systemic endotheliosis (Fucci²⁷⁷), depending on the author's concept of the origin of the monocytes.

270 Harbitz, F. Acute Atypical Military Tuberculosis, i. e., Without Distinct Macroscopical Findings and Presenting Picture of Lymphatic Leucaemia, *Acta path et microbiol Scandinav*, supp 26, 1936, p 173.

271 Jaffe, R. H. Nature of Anemia in Acute Leukemia, *Arch Path* **20** 725 (Nov) 1935.

272 Neumann, W., and Neugebauer, W. Scheinbare Blutgruppenänderung bei einem Leukämiekranken bei Unverträglichkeit von Blut eines sogenannten Universalspenders, *Med Klin* **32** 1067 (Aug 7) 1936.

273 Chini, V. Su di un caso complesso di emopatia (anemia a tipo pernicioso con splenomegalia, evoluzione leucemica a prevalente derivazione istioide e con spiccata megacariocitosi splenica), *Arch Ist biochim ital* **8** 127, 1936.

274 Kato, K. Hematology and Pathology of Leucemic Reticuloendotheliosis (Monocytic Leucemia) Occurring in Eighteen-Month-Old Infant, *J Pediat* **8** 679, 1936.

275 Reich, C. Case of Aleukemic Reticuloendotheliosis, *M Rec* **144** 84 (July 15) 1936.

276 Ramsey, T. L., and Tank, R. A. Acute Monocytic (Histiocytic) Leukemia, *Ohio State M J* **32** 637, 1936.

277 Fucci, N. Sulle iperplasie del sistema reticolo-istiocitario contributo allo studio della endoteliosi sistemica aleucemica, *Minerva med* **2** 4 (July 7) 1936.

A case of monocytic leukemia together with its medicolegal features was discussed in *The Journal of the American Medical Association* ²⁷⁸ A man with monocytic leukemia sustained an injury, gangrene of the leg and septicemia developed, and he died. In deciding the immediate cause of death and the financial responsibility, the court pointed out that under the Workman's Compensation Act, section 5223, "in case of aggravation of a pre-existing disease, compensation should be allowed only for such proportion of the disability or death due to the aggravation of such pre-existing disease as may be reasonably attributed to the injury on which the claim is based." Payment, then, was based on the shortening of the time that a patient with monocytic leukemia may be expected to live.

Among the various types of cells which may form a chloroma is the monocyte. A striking case was described by Gump, Hester and Lohr,²⁷⁹ that of a man aged 55 years. The lesion produced marked exophthalmos, first unilateral, later bilateral. There was no marked improvement after roentgen irradiation. The leukocyte count varied from 15,000 to 26,000 per cubic millimeter, with from 20 to 62 per cent of the cells monocytes. There was a hemorrhagic tendency, with terminal pneumonia.

A case of monocytic leukemia in which cutaneous nodules were a feature has been described by Loveman.²⁸⁰

Leukemia in Children—The subject of leukemia in children was studied by Pierce²⁸¹ (41 children, with 16 autopsies). For 48.7 per cent of the children there was a history of antecedent infectious illness from which there was failure to recover normally before the advent of the leukemic symptoms. Three types of patients were noted clinically: (1) those with a fulminating course and classic symptoms, (2) those with a less rapidly fatal course and with clinical and hematologic aspects which may be confused with leukemoid states or other blood dyscrasias and (3) those with a prolonged period of illness marked by relapses and remissions and a fluctuating blood picture. The aleukemic phase in this group of disorders may have certain clinical and pathologic features in common with those of malignant neutropenia.

An extensive review of acute leukemia in infants has been given by Lereboullet and Baize.²⁸²

²⁷⁸ Workmen's Compensation Acts. Death in Relation to Trauma and Pre-existing Leukemia, *Medicolegal Abstracts*, J A M A **107** 308 (July 25) 1936.

²⁷⁹ Gump, M E, Hester, E G, and Lohr, O W. Monocytic Chloroma (Reticulocytoblastoma with Monocytic Leukemia), *Arch Ophth* **16** 931 (Dec) 1936.

²⁸⁰ Loveman, A B. Monocytic Leukemia Cutis. Report of a Case with Biopsy Studies, *South M J* **29** 357, 1936.

²⁸¹ Pierce, M. Childhood Leucemia, *J Pediat* **8** 66, 1936.

²⁸² Lereboullet, P, and Baize, P. La leucemie aigue chez l'enfant, *Sang* **10** 279, 1936.

Morris and Hurwitz²⁸³ noted the leukemic state in 2 infants who were convalescing from pertussis

Differential Diagnosis—In the differential diagnosis of leukemia and infectious mononucleosis, the absence of agglutination of sheep corpuscles by the patient's serum (so-called heterophile antibody test) is of great value if the patient has not had serum infection or serum sickness. Agglutination, in a dilution of 1:128, establishes a diagnosis of infectious mononucleosis. Kracke and Garver,²⁸⁴ in pointing out this feature, also warned against confusing immature blast forms with lymphocytes.

Splenic puncture has been used by Emile Weil, Isch-Wall and Perlès²⁸⁵ to diagnose cryptoleukemia. This is myeloid, lymphatic or leukoblastic leukemia in which the peripheral blood is essentially normal but in which the internal organs show the character of the disease.

Treatment—The beneficial effects of potassium arsenite in chronic myelogenous leukemia have been studied by Stephens and Lawrence²⁸⁶ in 7 patients. Solution of potassium arsenite U. S. P. was given rapidly in doses of from 10 to 30 or more drops a day until toxic symptoms appeared. The maintenance dose was as large as could be tolerated. Transfusions and roentgen therapy were used when indicated. The effects noted were (a) symptomatic improvement, (b) a reduction in the size of the spleen, (c) a decrease in the total white blood cell count, (d) a decrease in the number of immature cells and in the number of immature red blood cells in the peripheral blood, (e) an improvement in the anemia and (f) an increase in the number of platelets. The treatment may be continued indefinitely, but relapses may take place during the course of therapy.

Albuminuria in leukemia is favorably affected by roentgen irradiation, according to Solomon,²⁸⁷ and he advised systematic irradiation of the kidneys before treatment of the spleen, bone marrow or glandular areas is begun.

No hematologic improvement was noted in leukemic patients by Meyer, Middleton and Thewlis²⁸⁸ after the administration of beef lymph

283 Morris, M., and Hurwitz, S. Myelogenous Leukemia in Infancy. Report of Two Cases Following Pertussis, *Arch. Pediat.* **53**: 367, 1936.

284 Kracke, R. R., and Garver, H. Laboratory Findings in Leukemic States, *Am. J. M. Technol.* **2**: 81, 1936.

285 Weil, P. E., Isch-Wall, P., and Perlès, S. Les cryptoleucémies, *Presse méd.* **44**: 41 (Jan. 8) 1936.

286 Stephens, D. J., and Lawrence, J. S. The Therapeutic Effect of Solution of Potassium Arsenite in Chronic Myelogenous Leukemia, *Ann. Int. Med.* **9**: 1488, 1936.

287 Solomon, I. Ueber die Behandlung und Prognose der Leukamien, insbesondere die günstigen Erfolge bei der nur die Milz betreffenden Form der lymphatischen Leukämie, *Strahlentherapie* **56**: 526, 1936.

288 Meyer, O. O., Middleton, W. S., and Thewlis, E. W. Therapeutic Failure with Certain Organic Substances in Leukemia, *Folia haemat.* **53**: 166, 1935.

nodes, beef duodenum, hog spleen and beef bone marrow by mouth or after the administration of extracts of the last three substances parenterally

O'Brien²¹¹ studied the effects of roentgen therapy on the leukemias. Fifty per cent of the patients with lymphatic leukemia did not live longer than three and three-tenths months after therapy was begun. The average duration of life after roentgen therapy was fourteen and six-tenths months. In chronic myelogenous leukemia it was twenty-one and nine-tenths months. There was no convincing evidence that irradiation prolonged life, as some patients had a slow type whereas others had a more fulminating type of the disease.

INFECTIOUS MONONUCLEOSIS

Although not generally recognized, infectious mononucleosis has been known as a disease entity since 1885, when Filatow described the disease as an idiopathic lymphadenopathy. A similar disease occurring in children was observed by Pfeiffer in 1889 and termed by him glandular fever. The importance of the glandular involvement was stressed by Desplats in 1894. In the same year Horschelmann emphasized the appearance of a scarlatina-like eruption during the course of the disease. Sprunt and Evans in 1920 and Longcope in 1922 established the disease on a more secure clinical basis and termed it infectious lymphocytosis and infectious mononucleosis, respectively.

Dalley²⁸⁹ and Poole and Findlay²⁹⁰ reviewed the literature and adequately described the essential features concerning the etiology, pathology and clinical course of this disease. Various organisms have been isolated and described as the etiologic factor of infectious mononucleosis, but none of them has ever been confirmed by any except the original investigators. Usually the disease occurs in either sex at any age, although it is much more common in children and in persons under 40 years of age. There are three types with various clinical features and differences in the length of the prodromal periods. In the glandular type the prodromal period is from one to four days, and in the angiose type, from one to three weeks. The average period of incubation is seven or eight days.

The more common symptoms observed are headache, general malaise, sore throat, tenderness of the lymph nodes, backache, chilliness, anorexia, coryza, sweating, weakness, cough, dizziness, soreness and bleeding of the gums, nausea, stiff neck, epistaxis, stomatitis, abdominal pain, rash, photophobia and conjunctivitis. The physical signs usually encoun-

²⁸⁹ Dalley, G. An Attack of Glandular Fever, *St Barth Hosp J* **43** 98, 1936.

²⁹⁰ Poole, L. T., and Findlay, H. T. Laboratory Diagnosis of Glandular Fever (Infectious Mononucleosis), *J Roy Army M Corps* **66** 145, 1936.

tered are fever, enlargement and tenderness of the nodes, injection of the throat, enlargement of the spleen, enlargement of the tonsils, membranous angina and a maculopapular rash

The complications which may be encountered are variable Dalley stated that the most usual ones are sepsis, hemorrhages, hematuria, purpura, conjunctivitis, jaundice, appendicitis, meningismus and involvement of the respiratory tract

An elevated white blood cell count of varying degree is encountered at some time during the course of the illness, leukopenia may occur at the onset The red blood cell count and the hemoglobin content are within normal limits The exact classification of the atypical mononuclear cells observed is difficult, and although most authors are of the opinion that the cells are of the lymphocytic group, there are many opponents of this view Freeman²⁹¹ reported 2 cases of typical infectious mononucleosis and gave observations on the bone marrow He stated that the marrow spaces are filled with the typical cells (immature lymphocytes) which are present in the peripheral blood

Downey and Stasney²⁹² described a fairly characteristic picture in nodes which were removed for biopsy during various periods of the acute illness Grossly the nodes are of variable size, soft and spongy, with a distended white capsule At the height of the disease there is extreme hyperplasia of the lymphoid tissue and the reticulum There is a dense aggregation of atypical basophilic lymphocytes, which suggests early leukemia, but there is never complete obliteration of the structure of the node, nor is there any invasion of the capsule In the advanced stages the germ centers and follicles have disappeared The irregularity of the hyperplasia of the reticulum and lymphoid tissue gives the node a characteristic nodular and spotty appearance Transitional stages between normal and atypical lymphocytes have been observed The cells present in the nodes are the same as those described in the bone marrow and peripheral blood In the author's opinion many of the atypical characteristics of the lymphocytes may develop after these cells enter the circulating blood Downey and Stasney concluded that the histologic and cytologic pictures are suggestive of a leukemoid reaction to an infectious toxic lymphotropic agent which is present in the lymph nodes

The prognosis is good, though relapses and remissions are not uncommon Apparently the disease is self-limiting The course may be protracted, and both glandular and hematopoietic changes may persist for many months The diagnosis can usually be based on the presence of the painful nodes and the characteristic changes in the

291 Freeman, W Bone Marrow Studies in Glandular Fever (Infectious Mononucleosis), *Am J Clin Path* 6 185, 1936

292 Downey, H, and Stasney, J The Pathology of the Lymph Nodes in Infectious Mononucleosis, *Folia haemat* 54 417, 1936

blood Poole and Findlay substantiated the specificity of the heterophilic antibody test, which was originally described by Paul and Bunnell Stuart Griffin, Fulton and Anderson²⁹³ also confirmed the value of this test, but in their opinion the antibodies are not of the Forssman type, as was previously suggested by other investigators

AGRANULOCYTOSIS

Interest in agranulocytosis during the past year has continued to center about the rôle of certain drugs as etiologic factors in the causation of the disease The theory that aminopyrine may be responsible for the disease in certain susceptible persons has received fairly widespread acceptance It is known, however, that many persons may take large amounts of the drug without producing the syndrome Nor is it the sole etiologic agent, as other drugs, such as dinitrophenol, apparently have been responsible for its production in some instances

Another point of interest in regard to the condition is our impression that the incidence of the disease is decreasing, although there is no definite evidence that the sale to the public of aminopyrine alone or in combination with other drugs is decreasing

Although all observers are not in accord, Rawls²⁹⁴ claimed that sufficient data have been accumulated to indicate that aminopyrine bears some causal relationship to agranulocytosis He administered over 100,000 tablets of aminopyrine or aminopyrine mixed with magnesium carbonate to 400 patients in clinic or in private practice In 4 (1 per cent) of these patients agranulocytosis developed, and 3 died of it Exclusive of the 4 patients, there were no significant changes in the white blood cell count or polymorphonuclear neutrophil percentages of 100 patients who received a mean daily dose of about 13 grains (0.85 Gm) for a mean interval of approximately eighty-four days It is considered that aminopyrine does not produce hematologic changes except in isolated cases, in which there probably is an idiosyncrasy to it

Nammack and Thorsteinson²⁹⁵ studied the blood of 100 patients with various diseases, chiefly rheumatism and infections of the upper respiratory tract who were treated with a combination of salicylic acid and antipyrine Antipyrine contains a benzene ring and is closely related in chemical structure to aminopyrine Repeated examinations of the

293 Stuart, C A, Griffin, A M, Fulton, M, and Anderson E G E Nature of the Antibodies for Sheep-Cells in Infectious Mononucleosis, *Proc Soc Exper Biol & Med* **34** 209 (March) 1936

294 Rawls, W B The Effect of Amidopyrin upon the Red, White and Polymorphonuclear Blood Cells of a Series of One Hundred Patients, *Am J M Sc* **192** 175, 1936

295 Nammack, C H, and Thorsteinson, N Study of One Hundred Cases with Administration of Drug (Salipyrine) Containing Benzene Ring, *New York State J Med* **36** 803 (May 15) 1936

blood of the patients did not show a significant change in the total white blood cell count or in the percentage of neutrophils, nor was there any change of importance in the Schilling count. From a review of the literature and their own experience the authors concluded that neutropenia in connection with drugs containing the benzene ring probably depends on individual idiosyncrasy to this type of drug.

Witts²⁹⁶ said that the evidence incriminating aminopyrine as the chief cause of agranulocytic angina may be classified as circumstantial, experimental and direct. He mentioned that in England the "Poisons List Confirmation Order" which went into force on May 1, 1936, makes it necessary to have a written order before aminopyrine can be supplied.

Parker and Kracke,²⁹⁷ in attempting to produce the disease experimentally, caused leukopenia (usually less than 1,000 leukocytes per cubic millimeter) in rabbits by the subcutaneous injection of benzene in olive oil and showed that these animals had a marked depletion of the biologically active or reduced glutathione in the bone marrow and the blood. They suggested that a depletion of this form of glutathione in human blood and bone marrow may lead to various leukopenic states.

Benjamin and Biederman²⁹⁸ reported observations on the blood of a subject after the oral administration of 10 grains (0.6 Gm) of novaldin (sodium phenyldimethylpyrazolon methylaminomethane sulfonate), a drug which is closely related to aminopyrine. This preparation was given to a woman aged 50, who previously had had several attacks of agranulocytosis after the ingestion of aminopyrine. Eight hours after the drug was given subjective symptoms appeared (chilliness and fatigue, followed by slight fever, headache and backache). Within twenty-four hours the white blood cell count had fallen from 5,300 to 2,800 per cubic millimeter, and the polymorphonuclear neutrophil cells had been reduced from 72 to 46 per cent. Intracutaneous, patch and passive transfer tests with novaldin gave negative results. The authors concluded that this drug may produce the same deleterious effects as aminopyrine on the hematopoietic system.

This view has been substantiated by Klumpp,²⁹⁹ who reported the case of a patient in whom agranulocytosis developed after the use of

296 Witts, L. J. (a) Prophylaxis and Treatment of Agranulocytosis, *Brit M J* **1** 1061 (May 23) 1936, (b) Effect of Toxic Substance on Blood-Forming Organs, with Special Reference to Therapeutic Drugs, *ibid* **2** 211 (Aug 1) 1936.

297 Parker, F. P., and Kracke, R. R. Further Studies in Experimental Granulopenia, with Particular Reference to Sulphydryl (Glutathione) Metabolism in Blood Dyscrasias, *Am J Clin Path* **6** 41, 1936.

298 Benjamin, J. E., and Biederman, J. B. Agranulocytic Leukopenia Induced by a Drug Related to Aminopyrine, *J A M A* **107** 493 (Aug 15) 1936.

299 Klumpp, T. G. Agranulocytosis Associated with the Administration of "Novaldin," a Derivative of Aminopyrine, *J A M A* **108** 637 (Feb 20) 1937.

this drug for headache. The patient succumbed after a fulminating illness of six days, during which time he had the characteristic symptoms of agranulocytosis. Examination of the blood showed red blood cells, 5,000,000, hemoglobin, 90 per cent and white blood cells, 150, per cubic millimeter. Examination of the smear showed only 20 leukocytes, and 18 of these were lymphocytes and 2 were monocytes. There was no response to treatment with liver extract, pentnucleotide and blood transfusions. Pathologic examination showed, in addition to an acute necrotizing process in the mouth and throat, hypoplasia of the bone marrow.

Goldman and Haber³⁰⁰ reviewed the literature concerning the relation between dinitrophenol and granulopenia and added the report of an additional case which they observed. Their patient, a girl of 13 years, had taken 0.1 Gm. of the drug daily for forty-six days. At the end of this time she had lost 25 pounds (11.5 Kg.). The following symptoms then appeared: weakness, malaise, feverishness, sore throat and vomiting. Examination showed the patient to be acutely ill and irrational. The throat was deeply injected, and a purulent exudate was present on the tonsils and uvula. The submaxillary glands were palpable and tender. The temperature was 105.6 F., the pulse rate, 136, and the respiratory rate, 32 per minute. Examination of the blood showed hemoglobin, 88 per cent, red blood cells, 4,600,000, white blood cells, 700, lymphocytes, 100 per cent, and platelets, 180,000. The DeRien test of the urine for dinitrophenol gave positive results. A direct smear of the throat showed gram-positive cocci, and culture yielded *Streptococcus viridans* of the alpha type. Death resulted after a rapid, fulminating course of a few days, despite the administration of liver extract intravenously and intramuscularly, a blood transfusion, the use of the oxygen tent and finally tracheotomy. Autopsy failed to reveal any changes in the granulopoietic system. The authors stated that their case is the fourth one to be reported which could be attributed to dinitrophenol. The three other patients recovered after withdrawal of the drug and the use of such measures as pentnucleotide, roentgen therapy, blood transfusions, injections of leukocytic cream and various supportive measures.

The bone marrow of 24 patients who died of agranulocytic angina was studied by Darling, Parker and Jackson.³⁰¹ They divided the subjects into three groups, as follows: those who died within four days of the clinical onset of the condition, those who died from five to ten days after the beginning of their illness and those in whom death occurred after an illness of more than ten days. The changes found were so uniform in the bone marrow that the authors considered the

300 Goldman, A., and Haber, M. Acute Complete Granulopenia with Death Due to Dinitrophenol Poisoning, *J. A. M. A.* **107** 2115 (Dec 26) 1936.

301 Darling, R. C., Parker, F., Jr., and Jackson, H., Jr. Pathological Changes in the Bone Marrow in Agranulocytosis, *Am. J. Path.* **12** 1, 1936.

condition a disease entity. The patients with rapidly fatal agranulocytic angina showed lack of maturation in the granular series and hyperplasia of the stem cells. Those who had had a longer illness usually showed hypoplasia of the myeloid tissue, with the coincidental appearance of many plasma cells and lymphocytes. The recovery stage is described as characterized by rapid development of the stem cells into melocytes, metamyelocytes and polymorphonuclear neutrophil cells. These changes, in the authors' opinion, substantiate the previous contention of other investigators that the condition in the bone marrow is one of arrested maturation.

There have been no striking contributions to the treatment of agranulocytosis during the past year. Perhaps the most important therapeutic measure is the avoidance of aminopyrine and closely allied drugs in the treatment of patients with agranulocytosis or those who have previously had the disease. Murphy³⁰² considered that sufficient evidence is not available to establish the intramuscular use of liver extract as the treatment of choice in agranulocytic angina but suggested that further experience may demonstrate that this preparation is as valuable in the control of this disease as it is in pernicious anemia. In Witts'^{296a} opinion pentnucleotide, transfusions, liver extract, arspenamine and roentgen treatment are not specific therapeutic agents.

BONE MARROW

The study of bone marrow is becoming more routine as to the differential diagnosis of blood dyscrasias. With only a few standards of "normal," the present material serves best as supplying data for the future evaluation of biopsy and autopsy material.

Jaffé³⁰³ summarized certain features of the study of marrow and described the condition in persons with normal marrow and in those with anemia, polycythaemia vera, agranulocytosis, leukemia, thrombocytopenia purpura, hemophilia or tumor of the bone marrow.

Higgins and Stasney³⁰⁴ found that after splenectomy in rats there was marked stimulation of the red blood cell-forming tissue, which reached its peak the second week after operation. This was accompanied with anemia. There was a contemporary depression of leukocyte-forming elements.

302 Murphy, W. P. Progress in the Treatment of Some Diseases of the Blood, *Minnesota Med* **19** 73, 1936.

303 Jaffe, R. H. The Bone Marrow, *J A M A* **107** 124 (July 11) 1936.

304 Higgins, G. M., and Stasney, J. Changes in the Bone Marrow and Peripheral Blood Following Splenectomy in White Rats. Preliminary Report, *Proc Staff Meet, Mayo Clin* **11** 446 (July 8) 1936, *Folia haemat* **56** 189, 1936.

Osgood and Muscovitz ³⁰⁵ and Osgood and Brownlee ³⁰⁶ have developed a method for allowing the survival and multiplication of bone marrow cells in vitro

An extensive study of bone marrow has been published by Segerdahl ³⁰⁷. The conditions in various diseases have been described by numerous authors. Wainright and Duff ³⁰⁸ have reported quantitative studies of the marrow of the femur and vertebrae in monocytic leukemia. Suárez ³⁰⁹ has studied the sternal bone marrow of normal persons and of persons affected with uncinariasis, sprue, Banti's disease and Schistosomum Manson, comparing the numbers of cells with those of venous blood. Carnot, Lavergne and Mallarmé ³¹⁰ found the study of bone marrow useful in the differential diagnosis of leukemia and myeloma. Totterman ⁸¹ and Lowinger ⁸² have reported details of the marrow in hemolytic jaundice. Jones ³¹¹ gave the results of biopsies of bone marrow of patients with pernicious anemia during a relapse. Heilbrun, ¹³¹ using the section method, studied the marrow of a patient with macrocytic anemia of pregnancy. Darling, Parker and Jackson ³⁰¹ presented the findings in agranulocytosis. Rosenthal and Grace ³¹² noted the changes due to radium poisoning in rabbits. Tecilazic ³¹³ studied the conditions in normal infants.

Details of the technic of obtaining bone marrow have been given by Karavanov, ³¹⁴ van der Merwe ³¹⁵ and others. Van der Merwe used

305 Osgood, E. E., and Muscovitz, A. N. Culture of Human Bone Marrow Preliminary Report, J. A. M. A. **106** 1888 (May 30) 1936

306 Osgood, E. E., and Brownlee, I. E. Culture of Human Bone Marrow A Simple Method for Multiple Cultures, J. A. M. A. **107** 123 (July 11) 1936

307 Segerdahl, E. Ueber Sternalpunktionen, Acta med. Scandinav., supp. 64, 1935, p. 1

308 Wainright, C. W., and Duff, G. L. Monocytic Leukemia, Bull. Johns Hopkins Hosp. **58** 267, 1936

309 Suarez, R. M. Comparative Study of Sternal Marrow Aspirated During Life and Venous Blood (Preliminary Report), Bol. Asoc. med. de Puerto Rico **28** 87, 1936

310 Carnot, P., Lavergne, H., and Mallarmé. A propos de la myelographie chez l'adulte, Compt. rend. Soc. de biol. **121** 314, 1936

311 Jones, O. P. Cytologic Studies of Biopsied Pernicious Anemia Bone Marrow During Relapse, Proc. Soc. Exper. Biol. & Med. **34** 694, 1936

312 Rosenthal, M., and Grace, E. J. Experimental Radium Poisoning Bone Marrow and Lymph-Node Changes in Rabbits, Produced by Oral Administration of Radium Sulphate, Am. J. M. Sc. **191** 607, 1936

313 Tecilazic, F. Ricerche ematologiche "in vivo" sul midollo osseo nella prima infanzia. Il midollo osseo nel lattante in condizioni normali, Pediatria **43** 1046, 1935

314 Karavanov, G. A propos de la technique de la ponction de la moelle osseuse pendant la vie, Sang. **10** 562, 1936

315 van der Merwe, C. F. Bone Marrow Studies in the Clinic, Folia haemat. **55** 108 and 218, 1936

the puncture aspiration method, somewhat like that of Osgood. He reported data on the marrow of persons with pernicious anemia, carcinoma of the stomach, chlorosis, steatorrhea, familial hemolytic jaundice, infectious mononucleosis, syphilis and aplastic anemia.

Huggins, Blocksom and Noonan³¹⁶ and Huggins and Blocksom³¹⁷ found that fatty marrow of rats could be transformed into actively hematopoietic tissue by raising the temperature. Studies were made of the marrow of the rabbit, the pigeon and the albino rat.

HEMATOLOGIC TECHNIC

It is doubtful that during the past year any real advances have been developed in the technic of examination of the blood. Numerous modifications of existing methods have been proposed, but for the most part their merits remain to be impartially demonstrated. In any laboratory certain refinements of procedure or apparatus will be found peculiarly adapted to local conditions.

Although not strictly a matter of technic, accumulated data relative to normal values find a natural place in the consideration of methods of hematologic examination. Such data have been compiled by Andresen and Mugrage,³¹⁸ Belk, Curtis and Wilson,³¹⁹ Fiddes and Whitney,³²⁰ and Bethell.¹²⁷ Quantitative observations on the blood lend themselves especially well to statistical analysis and interpretation. The standard deviations and coefficients of variation of erythrocyte counts made on identical blood samples by mechanical means and by eye were calculated by Magath, Berkson and Hurn.³²¹ By Fisher's methods of analysis

316 Huggins, C. B., Blocksom, B. H., Jr., and Noonan, W. J. Experiments on the Distribution of Red Bone Marrow, *J. A. M. A.* **106** 325 (Jan 25) 1936, Temperature Conditions in the Bone Marrow of Rabbits, Pigeon, and Albino Rat, *Am. J. Physiol.* **115** 395, 1936.

317 Huggins, C. B., and Blocksom, B. H., Jr. Changes in Outlying Bone Marrow Accompanying Local Increase of Temperature Within Physiological Limits, *J. Exper. Med.* **64** 253, 1936.

318 Andresen, M. I., and Mugrage, E. R. Red Blood Cell Values for Normal Men and Women, *Arch. Int. Med.* **58** 136 (July) 1936. Mugrage, E. R., and Andresen, M. I. Values for Red Blood Cells of Average Infants and Children, *Am. J. Dis. Child.* **51** 775 (April) 1936.

319 Belk, W. P., Curtis, E., and Wilson, M. K. Erythrocyte Counts, Hemoglobin, and Erythrocyte Volume in Normal Young Men and Women Residing in the Eastern United States, *Am. J. Clin. Path.* **6** 487, 1936.

320 Fiddes, J., and Whitney, C. Erythrocyte Count and Haemoglobin Percentage in the Blood of Adult Males in Saskatchewan, *Canad. M. A. J.* **35** 654, 1936.

321 Magath, T. B., Berkson, J., and Hurn, M. Error of Determination of Erythrocyte Count, *Am. J. Clin. Path.* **6** 568, 1936.

of variance Rosahn and Casey³²² found statistically significant differences in the blood formulas of 5 healthy men and of 6 healthy rabbits. They concluded that each individual possesses a characteristic blood picture, largely determined by genetic factors, and that a formula normal for one subject may signify abnormality in the case of another.

A modification of the congo red method of estimating plasma and total blood volume has been described by Olloz³²³. By the use of a photometer and a special injection technic, the quantity of dye injected can be reduced to 3.5 cc of a 1 per cent solution, thus permitting frequently repeated determinations. Hedenius³²⁴ has devised an apparatus for measuring the coagulation time by the observation of a transparent bead moving in a tube containing blood. The motion of the bead stops as soon as coagulation begins. Sharp and Schleicher³²⁵ reported their results obtained with Bock's erythrocytometer in the measurement of the diameters of red blood cells and concluded that this method, based on halometry, gives approximately the same values for the mean diameter of erythrocytes as those obtained with the Echelon ocular micrometer, with the advantage of being much less time consuming.

As an incentive to the display of inventiveness the enumeration and classification of platelets is rivaled only by the attractions of the sedimentation rate. A modification of Rahdenburg's method of counting platelets has been devised by Danilin,³²⁶ a diluent, a 3 per cent solution of sodium citrate, thirty-eight parts, and 1 per cent malachite green, one part, being used. For the count a red blood cell pipet is employed, and the platelets and erythrocytes are enumerated successively in the counting chamber. Leslie and Sanford³²⁷ described a method of quantitative and qualitative estimation of platelets in their own plasma, depending on a consideration of the coagulation times of whole plasma, platelet-free plasma and platelet-rich plasma. Olef³²⁸ continued his investigations of platelets and differentiated them into four groups

322 Rosahn, P. D., and Casey, A. E. Quantitative Variations in Hemacytologic Constitution of Healthy Men and Rabbits, *Am J M Sc* **192** 456, 1936

323 Olloz, M. Zur Methodik der wiederholten Blutmengenbestimmung, *Deutsches Arch f klin Med* **178** 647, 1936

324 Hedenius, P. Apparatus for Determining Coagulation Time of Blood, *Acta med Scandinav* **88** 440, 1936

325 Sharp, E. A., and Schleicher, E. M. Bock's Erythrocytometer and Technic for Its Use, *J Lab & Clin Med* **21** 975, 1936

326 Danilin, J. J. Eine neue Methode der Thrombocytenzahlung, *Folia haemat* **55** 82, 1936

327 Leslie, E. I., and Sanford, H. N. Method of Quantitative and Qualitative Estimation of Platelets in Their Own Plasma, *J Lab & Clin Med* **21** 1078, 1936

328 Olef, I. Differential Platelet Count. Its Clinical Significance, *Arch Int Med* **57** 1163 (June) 1936

according to size. He found in cases of thrombocytosis and in some conditions associated with thrombopenia an absolute or relative increase in the number of small platelets, considered juvenile, which possess high agglutinating properties. Incidentally, Olef's technic of enumerating platelets, an indirect method employing a fresh wet preparation of diluted blood, has in our experience proved eminently satisfactory as regards both accuracy and convenience.

New methods of determining the sedimentation rate of erythrocytes have been described by various investigators. Brooks³²⁹ devised a tube fitted to a venipuncture needle with a stopcock near the end of the needle. In this way, blood enters directly the calibrated tube, which is previously moistened with a solution of potassium oxalate. Smith³²⁰ developed a technic for the use of capillary blood that is especially adapted to determinations for infants and children but similar in principle to the macromethods in general use. A relatively simple photographic apparatus for the automatic and continuous recording of the sedimentation rate is described by Lee³³¹. He called it a sedimentometer. Sasano, Ordway and Medlar³³² studied certain extrinsic factors which may influence the sedimentation rate. Of these, temperature was most important, and they recommended that the test be made as a routine in an incubator at 37.5 C. Changes in barometric pressure produced slight but relatively insignificant differences. Manipulation of the blood should be reduced to a minimum, because of its effect on the suspension stability. Several anticoagulants were tested, and results closely agreeing with those secured with heparin were obtained by the use of a 1:1 per cent solution of potassium or sodium oxalate, one part of anticoagulant solution to three parts of blood. Capillary blood may be used, and a formula is provided for correction of the rate according to the volume of packed cells. A general review of the subject of the sedimentation test, including a detailed exposition of his own method, has been published by Wintrobe³³³.

329 Brooks, C. New Method and New Pipette for Blood Sedimentation, *J Lab & Clin Med* **21** 971, 1936.

330 Smith, C. H. Method for Determining Sedimentation Rate and Red Cell Volume in Infants and Children with Use of Capillary Blood, *Am J M Sc* **192** 73, 1936.

331 Lee, T. Sedimentometer Photographic Apparatus for Automatic Recording of Blood Sedimentation Rate, *Brit M J* **2** 809 (Oct 24) 1936.

332 Sasano, K. T., Ordway, W. H., and Medlar, E. M. Study of Certain Factors Which Influence Sedimentation Rates of Erythrocytes with Especial Emphasis upon Effect of Temperature, *Am J Clin Path* **6** 432, 1936.

333 Wintrobe, M. M. Erythrocyte Sedimentation Test, *Internat Clin* **2** 34, 1936.

Book Reviews

Diseases of the Air and Food Passages of Foreign-Body Origin By Chevalier Jackson, M D, and Chevalier L Jackson, M D Price, \$12 50 Pp 994, with 2,000 illustrations, including 3 plates in colors Philadelphia W B Saunders Company, 1936

This book is divided into two parts The first part is 333 pages long and is in reality a textbook of diseases of foreign body origin The second part is 636 pages long and tabulates the kinds of foreign bodies which the Jacksons have removed in 3,266 instances from the air or food passages of their patients, the location of each foreign body, the type of operative procedure carried out in its removal and the result of treatment in each case

To a medical layman unfamiliar with the authors' methods the volume as a whole is as exciting as a mystery story The chapters in the first part of the book are delightfully written and are full of practical details regarding the etiology, the symptoms and the physical signs of foreign body deposits in the air or food passages About half the textbook deals with such matters The other half deals with treatment and describes bronchoscopy, esophagoscopy and the manner in which foreign bodies can be removed from the air or food passages

The second part of the volume is equally engrossing It is composed of a series of tables, and with each table is a photograph of the foreign body described There is a short summary giving the patient's age, the nature of the foreign body, the anesthetic used in its removal, the problem presented, for instance, whether the safety pin in the larynx was open, pointed upward or embedded or whether the false teeth in the esophagus required version before they could be extracted, the result of the operative procedure, and the time required in its performance

A book of this scope and character is bound to be extremely useful Medical men will find it good reading for what it has to say from the point of view of the diagnosis of the various conditions it describes All surgeons interested in bronchoscopy or esophagoscopy will wish to read it, and those who actually are concerned with the removal of foreign bodies from the air or food passages will find it an indispensable *vade mecum*

Clinical Heart Disease By Samuel A Levine, M D Price, \$5 50 Pp 445, with 97 illustrations Philadelphia W B Saunders Company, 1936

The author of a textbook of medicine should be able to write clearly and concisely, should have something to teach and considerable experience in teaching it and should have a comprehensive experience covering the whole field about which he writes While embodying in his book the consensus of the best medical practice, he should not hesitate to state advanced ideas that have not yet received general acceptance but which have stood critical, practical tests in his own experience

Dr Levine has met these qualifications and has achieved this end in his textbook He writes in a conversational style, as though standing at the bedside of a patient and discussing the manifold aspects of a specific cardiac lesion However, this facile style is a little misleading, and it is easy for the reader to overlook some important points

The author announces his intention of writing a textbook for the general practitioner and then actually accomplishes this amazing feat No complicated system of classification or references are included The discussion of each type of cardiac disease includes sound advice as to treatment Careful perusal of the discussion *of the correct interpretation of a systolic murmur should lessen the tendency to make a diagnosis of valvular lesion without justification and conversely should reduce the likelihood of failure to recognize a significant systolic murmur*

The chapter on electrocardiography is clearly written and contains much of practical importance, but it is doubtful if the general practitioner will be able to use this technical information to any great extent.

Altogether Dr Levine's textbook will be of great value to the general practitioner, as well as to the physician who attempts to qualify as a specialist in the treatment of cardiac disease.

Klinik und Therapie der Herzkrankheiten und der Gefässerkrankungen

By D Scherf Third edition Price, 6 90 marks Pp 290, with 10 illustrations Vienna Julius Springer, 1936

The favorable reports given the previous editions of this volume may well be carried over to the third edition. The title has been changed to include the section on diseases of the blood vessels, which has been added to the text.

The discussion of peripheral vascular disease is brief, in keeping with the general trend of the book. Methods of investigation are first enumerated, such as observations on the temperature of the skin, oscillometry, the reactive test for hyperemia, tests of the reaction to histamine and roentgenographic visualization of vessels. A brief but lucid description of the essential features of each disease is then given.

In the domain of cardiac disease itself, several new sections add completeness to the survey of the subject. Congenital heart disease, pericarditis and bacterial endocarditis are considered. A section on the important types of arrhythmia has been added and rectifies a conspicuous omission in former editions. Extrasystoles, auricular fibrillation and the tachycardias, particularly paroxysmal tachycardia, receive the major consideration.

The general tone of the book remains unchanged. All additions, in keeping with the older material, are brief but well written.

Cushny's Pharmacology and Therapeutics Eleventh edition Revised by C W Edmunds, M D, and J A Gunn, M D, D Sc Price, \$6 50 Pp 808, with 70 illustrations Philadelphia Lea & Febiger, 1936

The reviewer, in a general way, disapproves of attempts to perpetuate a book by publishing revisions after the original author is dead. Often it seems as though the motive of the publisher is to retain the advertising value of a great name and that the man who revises the book could probably write a better text of his own. This criticism hardly applies, however, in the present instance, since from the nature of the subject any alteration from the original will be more in the way of additions than revisions. For example, the facts stated by Professor Cushny about morphine are probably as true today as they were at the time the first edition was published, and the task of bringing the book up to date is mainly one of describing agents which have been newly developed. One does not have the problem of a complete change of point of view, such as obtains in a clinical subject. It is a pleasure, therefore, to the reviewer to see again a new edition of this old friend in much the same format as the volume he labored over in student days.

The Study of the History of Science By George Sarton Price, \$1 50 Pp 75, with 6 illustrations Cambridge Harvard University Press, 1936

Nowadays in the program of medical education increasing emphasis is being placed on the history of medicine. Students, who heretofore were taught nothing of the lore of the medical guild, now often become first class amateur historians and, occasionally, are trained as professional historians by those schools fortunate enough to have a department of medical history.

Here is a booklet to delight the heart of any one with a historical bent. It sketches in barest outline what the study of the history of science means, how such a study is conducted and whither such a study may lead. It is charmingly written. It is the sort of volume that should be on the open shelves of every medical library as a particularly tempting morsel of bait to be gobbled up by hungry-minded students.

A Textbook of Surgery By John Homans, M D Fourth edition Price, \$8
Pp 1,267, with 530 illustrations Springfield, Ill Charles C Thomas,
Publisher, 1936

The difficulty in the past with textbooks of surgery has been that too much stress has been laid on operative technic, which is of little value to the medical student, who must learn technic in the laboratory and the operating room Dr Homans recognizes all this and frankly emphasizes diagnosis and general principles of therapy rather than controversial points on whether to cut and suture here or there The book, nicely published, well illustrated and entertainingly written, appeals to the reviewer as by far the most useful textbook of surgery he has seen for the medical student

Techniques chirurgicales By A Gosset Price, 125 francs Pp 434, with 219
illustrations Paris Masson et Cie, 1936

Professor Gosset and a group of his associates at the surgical clinic of the Salpêtrière have collaborated in preparing this publication, which includes a description of the important construction details and equipment incorporated in the new clinic building, an outline of the organization and functions of the laboratories, a chapter on sterilization of surgical supplies, a chapter on anesthesia and several chapters on surgical subjects selected at random The chapters on surgical subjects include general observations and reveal the management, especially the surgical procedures, applied at the Salpêtrière in selected types of cases

Differentialdiagnose in der inneren Medizin By Prof Dr Med O Naegeli
Price, 9 60 marks Pp 414, with 42 charts Leipzig Georg Thieme, 1936

This volume is one section of a larger work on differential diagnosis in internal medicine One naturally has respect for anything written by Professor Naegeli, but the reviewer doubts the value of dealing with differential diagnosis as an isolated subject, and this feeling is supported in the present instance It seems that the matter herein contained would be more useful if presented in connection with a complete discussion of the various diseases

Arbeit und Gesundheit Edited by Martineck Number 28 **Kreislauf-
krankheiten und Nierenkrankheiten bei Kriegsbeschädigten Häufig-
keit, Erscheinungsform und Verlauf** By Dr Ludwig Delius Price,
4 marks Pp 125, with 8 tables and 17 charts Leipzig Georg Thieme, 1936

This little volume deals with follow-up studies of patients who acquired nephritis or cardiac disease during the war The chief conclusion is that the nephritis ran the usual course of Bright's disease, 50 or 60 per cent of the patients recovering completely and the remainder showing chronic changes

Die Sternalpunktion als diagnostische Methode By Hans Schulten, M D
Price, 18 marks Pp 82, with 16 plates Leipzig Georg Thieme, 1937

This book gives an admirable discussion of the histologic picture of bone marrow The technic of obtaining material by sternal puncture is taken up in detail, and there are many excellent plates of marrow cells in various diseases

News and Comment

AMERICAN HEART ASSOCIATION, INC

The Thirteenth Scientific Session of the American Heart Association will be held on June 7 and 8, 1937, from 9 30 a m to 5 30 p m, in the Viking Room, Hotel Haddon Hall, Atlantic City, N J On Monday, June 7, the program of the Section for the Study of the Peripheral Circulation will be given The general program will be presented on Tuesday, June 8

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